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BRITISH MEDICAL JOURNAL

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RECENT STUDIES ON CARBOHYDRATE METABOLISM*

BY

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I wish to express my sincere thanks to the President and the Council of the Harveian Society of London for the honour they have done me in inviting me to give this year's Harveian Lecture.

While I deeply appreciated having the offer of this great privilege I had some considerable doubts in my mind of my qualifications for the task. Nearly all the previous Harveian lectures have been concerned with purely medical subjects, usually reviewing advances in some important field of clinical medicine, and, almost without exception, they were presented by famous physicians or surgeons. As you know, I am a biochemist by profession, without medical training, and, moreover, my personal biochemical interests have never been primarily concerned with problems of clinical medicine.

However, I finally found the courage to accept the invitation of the Harveian Society, mainly on the strength of the reflection that, after all, some major advances in modern medicine—for instance, much of the knowledge which led to the therapeutic use of vitamins, antibiotics, and some hormones—were the results of pure academic biochemical investigations which did not directly originate from the daily problems of the hospital ward, though I am very conscious of the fact that the primary impulse to these studies has usually been a biological or clinical observation, and that for some aspects of medical research the closest contact between the clinician and the biochemist is not only useful but essential for progress.

I have always been particularly interested in the elucidation of the biochemical mode of action of substances which display some characteristic biological action. This led me to the study of the mode of action of the neurotoxic principle contained in some snake venoms, and in collaboration with various colleagues, particularly H. W. (now Sir Howard) Florey and Dr. E. S. Duthie,† to the study of the biochemical mechanism of some lytic and permeability phenomena, and, as an expansion of those investigations, to the study of antibacterial substances produced by micro-organisms, now known as antibiotics, which resulted in the discovery of the curative power of Fleming's penicillin.

About 10 years ago I and my colleagues at the biochemistry department of the Istituto Superiore di Sanità (the Institute of Public Health of the Italian State) began an investigation into the mode of action of insulin, as part of a more general research programme on the mode of action of hormones. We felt that a deeper understanding of the mode of action of these substances, which, in minute amounts and in a specific manner, regulate the rates of metabolic reactions, was essential for further progress in the understanding and, eventually, the treatment of metabolic disorders, and therefore represented one of the most central and important fundamental problems of modern biochemistry.

*Harveian Lecture delivered to the Harveian Society of London on March 18, 1959.

†Dr. Duthie died suddenly in May, 1959. His untimely death has caused profound grief to myself and his many friends and is a great loss to science.

In-vitro Effect of Insulin on Glycogen Synthesis in Rat Diaphragm

We chose insulin for the start of this study because in 1949, when this work was initiated, at least one clear-cut *in-vitro* effect of insulin on an isolated tissue had been conclusively demonstrated: Gemmill (1940, 1941) had shown that in the isolated rat diaphragm insulin stimulates glucose uptake and glycogen synthesis. We thought that so much progress in the understanding of the reactions of intermediate carbohydrate metabolism had been made and so many new powerful analytical tools for its study had become available that it should either be possible to fit insulin into the existing reaction schemes, or else some new important reactions which had hitherto escaped attention would come to light.

The effect of insulin on glycogen synthesis and glucose uptake in the isolated rat diaphragm discovered by Gemmill was confirmed by a number of authors, including Villee and Hastings (1949), who were the first to use radioactive glucose for these studies. From the figures of these experiments, given in Table I, it is evident that only a small part of the glucose metabolized was recovered as glycogen and CO_2; the greater part was unaccounted for, and this "unaccounted for" fraction was greater in the presence of insulin than in its absence.

TABLE I.—*In-vitro Utilization of ^{14}C-labelled Glucose by Rat-diaphragm Muscle (after Villee and Hastings, 1949)*

	Normal		Diabetic	
	Without Insulin	With Insulin	Without Insulin	With Insulin
No. of animals	14	14	7	7
Total glucose disappearing from medium* (mg. g. hr.)	1·53 ± 0·046	2·87 ± 0·047	0·78 ± 0·035	2·17 ± 0·10
Glucose metabolized to CO_2* (mg. g. hr.)	0·11 ± 0·012	0·22 ± 0·026	0·08 ± 0·019	0·11 ± 0·030
Glycogen synthesized* (mg. g. hr.)	0·17 ± 0·052	0·62 ± 0·13	0·14 ± 0·045	0·61 ± 0·19
Glucose unaccounted for (mg. g. hr.)	1·25	2·03	0·56	1·45
Utilized glucose recovered as CO_2%	7·2	7·7	10·3	5·1
Utilized glucose converted to glycogen (%)	11·1	21·6	18·0	28·1
CO_2 in centre well derived from glucose in medium (%)	10·4	16·3	8·1	9·2

* The values given are means ± standard error.

Quantitative Radiochromatographic Techniques

My colleagues and I set ourselves the task of getting a quantitative balance-sheet of glucose metabolism in the isolated diaphragm of the rat in the absence and presence of insulin (Beloff-Chain, Catanzaro, Chain, Masi, Pocchiari, and Rossi, 1955a). After incubation of the muscle for various periods with generally labelled ^{14}C-glucose on other labelled substrates of carbohydrate metabolism, the radioactive metabolites in the incubation medium and the tissue were separated by suitable paper chromatographic methods and quantitatively determined. In addition, the CO_2 formed was collected and its radioactivity measured. The quantitative evaluation of the chromatograms was first done by hand, using the method of Fink, Dent, and Fink (1947), by passing paper strips under a Geiger counter and measuring the radioactivity per centimetre. This method proved too slow and tedious for monodimensional chromatograms, and impracticable for bidimensional chromatograms. Consequently it became necessary to develop automatic scanning methods. This was done in collaboration with Dr. M. Frank, of the electronics department of the institute. The older methods, described in previous publications from this department (Chain, Frank, Pocchiari, Rossi, Ugolini, and Ugolini, 1956), are now superseded by the latest model (Fig. 1) (Frank, Chain, Pocchiari, and Rossi, 1959).

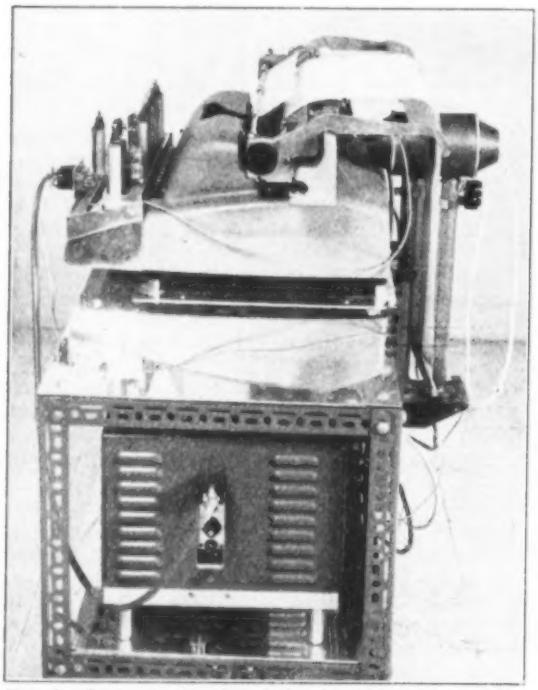

FIG. 1.—Automatic scanning device for bidimensional radiochromatograms (Frank *et al.*, 1959).

The scanning apparatus consists of an electric typewriter on the number of keys of which a series of solenoids is fixed, actuating them when energized. The radiochromatogram is fastened by Scotch-tape to a sheet of blank paper inserted into the carriage of the typewriter and is drawn by the movements of the typewriter carriage between two end-window Geiger counters attached to the back of the typewriter, thus exposing a unit square area of the radiochromatogram for counting for a period depending on the intensity of the radiations. If the radiation intensity of the unit area of the paper chromatogram exposed to the Geiger counters is below a certain arbitrarily chosen threshold value, this is considered background radiation and the typewriter carriage is held stationary for 45 seconds; if this threshold value is exceeded it is considered to be due to radioactive material and the typewriter carriage is maintained stationary for five times this period.

An electronic discrimination circuit transmits the number of counts, collected in the Geiger counters and counted in electronic counting-tubes, to the corresponding number keys of the typewriter, and at the end of the counting period the number is printed on the blank sheet in the typewriter carriage in the position corresponding to the position of the radioactive spot on the radiochromatogram; the typewriter carriage then moves on to the next position, and when the whole line is explored returns to its original position, simultaneously turning the roll so that the blank paper sheet and with it the paper chromatogram are moved toward the next line.

The time necessary for the complete evaluation of a bidimensional radiochromatogram depends on the radioactivity; under the experimental conditions used by us the evaluation of a bidimensional radiochromatogram of a tissue extract incubated with a ^{14}C- or ^{32}P-labelled metabolite takes about 16 hours. Six scanning machines are in continuous use in our laboratory; they function day and night, sometimes for weeks without interruption, and require very little maintenance.

A scanning device for monodimensional radiochromatograms using the same "read-out" method has also been devised (Fig. 2).

In this way "number maps" are obtained which give the quantitative distribution of the radioactive metabolites separated on the bidimensional radiochromatograms (Fig. 3). With this technique, each tissue after incubation with radioactive substrates was found to have a characteristic qualitative and quantitative metabolic pattern reflecting its biochemical functional state. Characteristic changes of this pattern are observed in pathological conditions and under the influence of hormones and drugs; on the basis of these changes deductions can be made of the nature of the

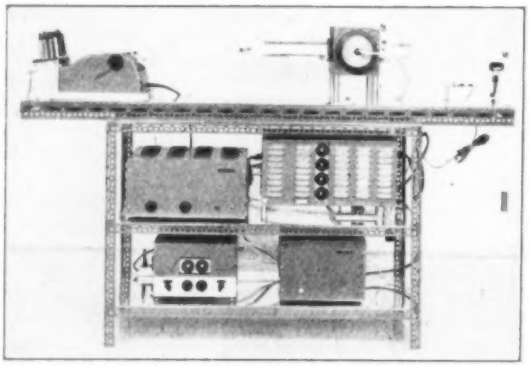

FIG. 2.—Automatic scanning device for monodimensional radiochromatograms.

FIG. 3.—Radioautograph and the corresponding number map of a bidimensional radiochromatogram.

"biochemical lesion" (Peters, 1936) on the point of attack of the pharmacologically active substances.

Action of Insulin on Glucose Metabolism in the Isolated Diaphragm Muscle of the Rat

Radioautograms of monodimensional radiochromatograms of the incubation medium and of an aqueous-alcoholic extract of exhaustively washed rat-diaphragm muscle after incubation for 90 minutes with uniformly labelled glucose are shown in Fig. 4. The main metabolite in the incubation medium was lactate; in addition triosephosphates were found. The tissue extract also contained lactate, though much less than the incubation medium; in addition, glucose, glycogen, and a number of oligosaccharides were found. The latter are better separated by bidimensional chromatography and were identified as maltose, maltotriose, and maltotetrose (Fig. 5). The insoluble residue of the muscle after extraction with aqueous alcohol was also radioactive; nearly all the radioactivity was accounted for as glycogen. Thus, the "unaccounted for" glucose in the table of Villee and Hastings (1949) was recovered as lactate, intracellular glucose, oligosaccharides, and insoluble glycogen.

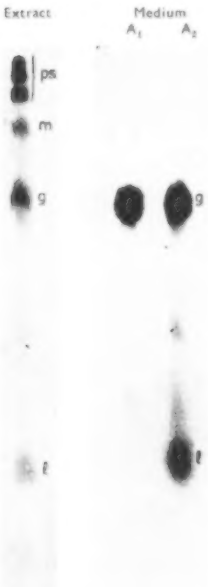

FIG. 4.—Radiochromatogram of aqueous-alcoholic extract of diaphragm muscle of the rat and media before and after incubation with ^{14}C-labelled glucose. A_1 = Medium before incubation. A_2 = Medium after incubation.

The effect of insulin on glucose metabolism in the rat diaphragm is shown in Table II. It will be seen that insulin has no effect on the CO_2 production and only very little, if any, effect on lactate production and the concentration of intracellular glucose. It has, however, a very great effect on the formation of glycogen and the oligosaccharides—that is, it has no effect on the energy-requiring anabolic reactions. This insulin effect takes place very rapidly, being already noticeable after only three minutes' incubation (Figs. 6 and 7).

Fructose (Beloff-Chain, Catanzaro, Chain, Masi, and Pocchiari, 1955b) forms the same metabolites in rat-diaphragm muscle as does glucose, but only half as much total fructose as glucose is metabolized, and the formation of glycogen and oligosaccharides is reduced to about one-seventh. CO_2 production and production of lactic acid from fructose are about the same as they are from glucose.

As in the case of glucose, insulin has no effect on the katabolic reactions of fructose, but a marked effect on the anabolic reactions leading to the formation of glycogen and oligosaccharides (Table III).

TABLE II.—*Influence of Insulin on Glucose Metabolism in Rat-diaphragm Muscle**

	No Insulin	With Insulin
Aqueous-alcoholic extract:		
Zone ps	10·4 ± 1·7	23·7 ± 2·8
,, m	3·0 ± 0·3	5·6 ± 0·7
,, g	18·0 ± 1·9	21·6 ± 2·0
Glycogen of insoluble residue	14·9 ± 4·3	25·4 ± 6·7
Zone I (sum of lactate in extract and medium)	24·8 ± 3·4	28·4 ± 4·9
CO_2	13·8 ± 1·9	13·6 ± 2·0

* Results expressed as μg. of glucose converted per 50 mg. of diaphragm muscle (wet weight) incubated in 0·6 ml. of phosphate buffered medium at *p*H 6·8 at 37° C. Glucose concentration 0·1%. Mean values of 8 experiments given ± S.E.M. (after Beloff-Chain *et al.*, 1955a).

FIG. 5.—Radiochromatogram of aqueous-alcoholic extract of diaphragm muscle of the rat incubated with ^{14}C-labelled glucose. (Two - dimensional chromatogram: ←butanol:ethanol:NH_3: water; ↓picric acid:tertiary butyl-alcohol:water.) (Beloff-Chain *et al.*, 1955a.)

TABLE III.—*Influence of Insulin on Fructose Metabolism in Rat-diaphragm Muscle**

	No Insulin	With Insulin
Aqueous alcoholic extract:		
Zone ps	1·4 ± 0·4	5·0 ± 0·9
,, m	0·7 ± 0·09	1·9 ± 0·2
,, f	27·4 ± 1·4	29·0 ± 3·2
Glycogen of insoluble residue	1·6 ± 0·3	3·3 ± 0·7
Zone I (sum of lactate in extract and medium)	31·4 ± 1·0	35·2 ± 0·4
CO_2	13·7 ± 1·1	13·6 ± 0·8

* Results expressed as μg. of fructose converted per 50 mg. of diaphragm muscle (wet weight) incubated in 0·6 ml. of phosphate buffered medium at *p*H 6·8 at 37° C. Fructose concentration 0·1%. Mean values of 4 experiments given ± S.E.M. (After Beloff-Chain *et al.*, 1955b.)

Action of Insulin on Glucose Metabolism in the Isolated Brown Adipose Tissue of the Rat

Active synthesis of glycogen and fat has been shown by Tuerkischer and Wertheimer (1942) to occur *in vivo* in the brown adipose tissue of the rat, and Wertheimer (1945) demonstrated that after injection of insulin the synthesis of glycogen in this tissue was greatly

stimulated. We followed the fate of uniformly labelled glucose in slices of brown adipose tissue of the rat with their quantitative radiochromatographic technique in the presence and absence of insulin (Beloff-Chain, Catanzaro, Chain, Masi, and Pocchiari, 1956a). As shown in Table IV, we found that glucose was converted into the same metabolites as it was in the isolated diaphragm muscle of the rat—that is, CO_2, lactic acid, oligosaccharides, and glycogen. In addition it was converted into fat. Insulin stimulated, as it did in the rat diaphragm, glycogen and oligosaccharide synthesis and, in addition, it greatly stimulated the synthesis of fat from glucose without influencing to any marked degree CO_2 and lactic acid production. Thus in the brown adipose tissue of the rat insulin was shown to stimulate two synthetic reactions—the synthesis of glycogen and oligosaccharides, and fat synthesis, the most endergonic of all metabolic syntheses.

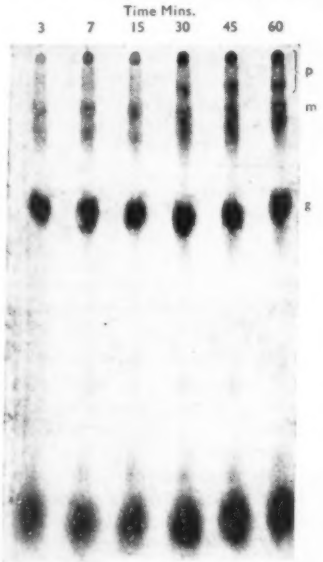

FIG. 6. — Radiochromatogram of aqueous-alcoholic extract of diaphragm muscle of the rat incubated for varying periods with uniformly labelled ^{14}C-glucose (Beloff-Chain *et al.*, 1955a).

TABLE IV.—*Influence of Insulin on Glucose Metabolism in Slices of Brown Adipose Tissue of the Rat**

	No Insulin	With Insulin
Aqueous alcoholic extract:		
Zone ps + m	1·0 ± 0·08	2·7 ± 0·4
,, g	12·9 ± 1·2	11·2 ± 1·3
,, al	7·7 ± 0·9	9·8 ± 1·5
Insoluble residue (fat)	8·1 ± 1·3	15·2 ± 1·6
Zone I (sum of lactate in extract and medium)	48·6 ± 6·3	69·3 ± 4·8
CO_2	52·0 ± 7·1	61·0 ± 6·7

* Results expressed as μg. of glucose converted per 50 mg. of diaphragm muscle (wet weight) incubated in 0·6 ml. of phosphate buffered medium at *p*H 6·8 at 37° C. Glucose concentration 0·1%. Mean values of 11 experiments given ± S.E.M. (After Beloff-Chain *et al.*, 1956a.)

Current Theories of Insulin Action

Two theories have been advanced for the mode of action of insulin—the "permeability" theory and the "hexokinase" theory. According to the first, widely accepted, theory, insulin acts by increasing the permeability of the cell to glucose; according to the second it stimulates the hexokinase reaction—that is, the formation of glucose-6-phosphate from adenosine triphosphate (ATP). In our view neither of these theories can be reconciled with the experimental facts.

Experiments Designed to Test the Permeability Theory

If insulin acted by increasing the permeability of the cell to glucose—that is, by increasing the glucose concentration inside the cell—it should be possible to simulate the insulin effect by increasing the concentration of glucose in the incubation medium, provided it could be shown that the intracellular concentration of glucose increased to about the same degree as the extracellular concentration. Fig. 8 gives the results of measuring the concentration of uniformly labelled ^{14}C-glucose in the rat diaphragm after incubation with increasing amounts of uniformly labelled ^{14}C-glucose and subsequent careful washing. An aqueous-alcoholic extract of the muscle was prepared, the glucose separated chromatographically on paper and determined by measuring its radioactivity. It will be seen that the "intracellular" glucose concentration increases linearly with the external glucose concentration in the incubation medium.

In Table V the effect of increasing the glucose concentration in the incubation medium on the different glucose metabolites formed by the rat diaphragm is shown. Unlike insulin, an increase of the external glucose concentration brings about a marked increase of CO_2 and lactic-acid production. Oligosaccharides and glycogen also increase when the concentration of glucose in the incubation medium is raised from 0.1 to 0.5% (actually the limiting glucose concentration at which a stimulating effect on oligosaccharide and polysaccharide synthesis is noted is about 0.3%), and in this respect the effect of raising the glucose concentration is the same as the insulin effect. However, beyond the concentration when the glucose polymerizing system is saturated no further increase of oligosaccharides and glycogen occurs, yet insulin produces a specific accelerating effect on oligosaccharide and glycogen

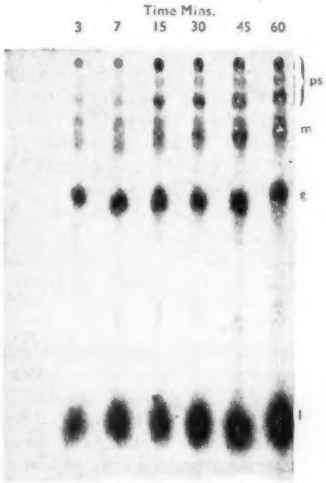

FIG. 7. — Radiochromatogram of aqueous-alcoholic extract of diaphragm muscle of the rat incubated for varying periods with uniformly labelled ^{14}C-glucose in the presence of insulin (Beloff-Chain *et al.*, 1955a).

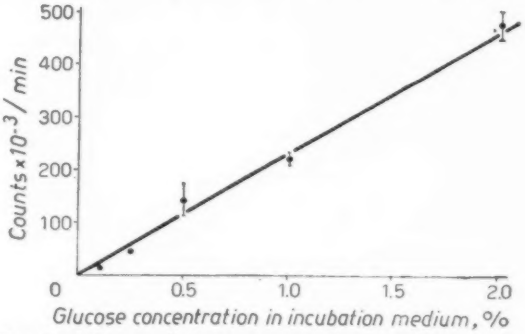

FIG. 8.—Influence of glucose concentration in medium on the intracellular glucose concentration of isolated diaphragm of the rat (Beloff-Chain *et al.*, 1956b).

TABLE V.—*Influence of Glucose Concentration on Distribution of ^{14}C from Uniformly Labelled Glucose in Diaphragm Muscle of Rat**

Glucose Concentration Fraction:	0·1%	0·25%	0·5%	1%
Aqueous-alcoholic extract:				
Zone ps ..	10·5 ± 3·3	21·0 ± 4·7	41·0 ± 3·7	42·0 ± 10·3
,, m ..	3·8 ± 0·6	9·5 ± 1·5	15·5 ± 3·0	17·0 ± 2·6
,, g	13·6 ± 1·3	46·5 ± 2·5	121·0 ± 32·0	221·0 ± 22·1
,, l	134·2 ± 10·4	202·0 ± 16·2	256·5 ± 31·2	275·0 ± 28·5
Glycogen of insoluble residue	8·0 ± 2·3	14·0 ± 2·9	16·5 ± 3·0	17·0 ± 4·4
CO_2	10·7 ± 8·0	14·0 ± 1·4	15·8 ± 1·7	19·5 ± 2·1

* Results expressed as c.p.m. $\times 10^{-3}$ (counted on paper) per 50 mg. of tissue, wet weight. Mean values of 6 experiments ± S.E.M. (After Beloff-Chain *et al.*, 1956b.)

synthesis even in the presence of 1% glucose (Fig. 9), again without influencing CO_2 and lactic-acid production. It is therefore clear that the effect on the pattern of glucose metabolism of increasing the glucose concentration is qualitatively and quantitatively different from the effect of insulin. Also, in the adipose tissue an increase of glucose concentration cannot simulate the insulin effect.

The permeability theory originated from experiments on eviscerated animals maintained at normal blood-sugar levels by continuous glucose infusion (Levine, Goldstein, Huddlestun, and Klein, 1950). The animals were injected with galactose, a sugar which at that time was thought not to be metabolized by muscle, and it was observed that insulin caused a fall of the blood-galactose concentration to a lower level, which then remained constant. In view of the assumed metabolic inertness of galactose these experiments were interpreted as indicating that insulin had caused an increased transfer from galactose into the muscle—that is, had increased the galactose space. Using radioactive galactose, it was shown (Beloff-Chain *et al.*, 1956b) that galactose actually is metabolized by muscle, though at a low rate, and therefore the basis of the theory is not valid.

However, in view of the particular conditions prevailing in eviscerated animals continuously infused with glucose, we decided to investigate with our quantitative radiochromatographic technique whether insulin did, in fact, stimulate galactose transfer in the isolated diaphragm muscle of the rat, in which it produces such marked stimulating effect on oligosaccharide and glycogen synthesis (Beloff-Chain *et al.*, 1956b). Again, aqueous-alcoholic extracts of rat diaphragms were prepared after incubation with radioactive galactose for different periods. Fig. 10 shows that only one radioactive spot, due to galactose, appears in radioautograms of monodimensional radiochromatograms of such extracts. The figures in Table VI demonstrate that the intracellular concentration of galactose is not affected by insulin after any time of incubation. Therefore, whatever the explanation of the experiments with eviscerated animals will turn out to be, insulin certainly does not lead to an increase of intracellular galactose in a tissue in which it has a pronounced effect on glycogen and oligosaccharides from glucose.

Apart from these experimental observations, it is difficult to see on thermodynamic grounds how an increase of the concentration of intracellular glucose, which even according to the supporters of the permeability theory can at best be only a small one, can possibly provide the energy required for the marked stimulation of fat by insulin synthesis, observed to occur in adipose tissue (Beloff-Chain *et al.*, 1956a) and the lactating mammary gland, in the latter not only from glucose but also from acetate in the presence of glucose (Balmain, French, and Folley, 1950; Balmain and Folley, 1951).

TABLE VI.—*Effect of Insulin on the Intracellular Concentration of Galactose-1-^{14}C in Isolated Rat Diaphragm**

Time of Incubation	Without Insulin	With Insulin
15 minutes	3,310 ± 110 (6)	3,340 ± 130
30 ,, ...	3,420 ± 120 (6)	3,370 ± 110
60 ,, ...	3,200 ± 220 (12)	3,320 ± 190
90 ,, ...	3,140 ± 220 (8)	3,620 ± 400

* Results expressed as radioactivity of galactose c.p.m. per 50 mg. of tissue, wet weight. Diaphragm incubated in O_2 at 37° C. in 0·6 ml. of phosphate saline medium. Galactose concentration in medium, 0·1%. Total radioactivity, 1 μc per Warburg vessel; approximately 7×10^4 c.p.m. (counted on paper). Number of experiments given in parentheses. (After Beloff-Chain *et al.*, 1956b.)

Experiments to Test the Hexokinase Theory

The fact that increasing the glucose concentration does not produce the same effect on the pattern of glucose metabolism in the rat diaphragm and in the adipose tissue as does insulin really excludes the hexokinase theory of insulin action, for if glucose itself does not simulate the specific effects of insulin, glucose-6-phosphate, believed to be the first product of glucose metabolism, also would not be expected to do so. Furthermore, as it is generally accepted that the muscle aerobically oxidizes glucose, but anaerobically converts it to lactic acid, and as the hexokinase reaction is thought to be involved under both these conditions, it was considered that if insulin acted by stimulating the hexokinase reaction it should prove possible to demonstrate an effect of insulin under anaerobic conditions. A study of the fate of glucose under anaerobic conditions in the diaphragm muscle of the rat was therefore undertaken, using the quantitative radiochromatographic technique referred to above (Beloff-Chain, Catanzaro, Chain, Longinotti, Masi, and Pocchiari, 1959a). The figures in Table VII show that under anaerobic conditions no oligosaccharide and glycogen synthesis took place in the rat diaphragm either in phosphate or on

FIG. 9.—Radioautograph of chromatogram of aqueous-alcoholic extract of diaphragm muscle of the rat incubated for 90 minutes with 1% glucose, with and without insulin.

FIG. 10.—Radioautograph of chromatogram of aqueous-alcoholic extract of diaphragm muscle of the rat incubated for 30 minutes with 0.1% galactose, with and without insulin.

bicarbonate buffer. Hence the reactions which are specifically stimulated by insulin do not take place under anaerobic conditions.

However, a number of interesting new facts regarding anaerobic glucose metabolism were brought to light. Intracellular glucose accumulated under anaerobic conditions irrespective of whether the rat diaphragm was incubated in phosphate or bicarbonate buffer. Contrary to expectation, lactic-acid formation from glucose under anaerobic conditions was not increased, but was often decreased to about half or less than half the aerobic value, again irrespective of the incubation medium. However, when the rat diaphragm was first incubated in oxygen with glucose for a short time and then put in anaerobic conditions, a spurt of lactic-acid production occurred, leading to the formation of more lactic acid than under aerobic incubation conditions for the same period (Table VIII, experiment 1). This spurt was of short duration, lasting for not more than two to three minutes.

When the tissue was incubated under aerobic conditions first with non-radioactive glucose and then radioactive glucose was added after five minutes' anaerobiosis, lactic-acid production was reduced to the normal small amount formed under anaerobic conditions (Table VIII, experiment 3). The presence of glucose in the aerobic phase was necessary. Addition of radioactive glucose after aerobic incubation of rat diaphragm in the absence of glucose did not lead to increased lactate production (Table VIII, experiment 2). A short contact of the tissue with oxygen in the presence of glucose for only three minutes was sufficient to produce the spurt (Table VIII, experiment 4). In fact, the lactic-acid spurt occurred when the glucose was added to the chilled incubation medium and the tissue in the central chamber of Warburg vessels before the equilibration with nitrogen. Therefore, unless the radioactive glucose is added from the side arm of the Warburg vessel to the tissue after anaerobic conditions have been created, erroneous conclusions may be drawn regarding the intensity of anaerobic glycolysis.

The mechanism of the lactic-acid spurt is not understood, but two possible hypotheses can be suggested. Either some factor in the glycolysis system was irreversibly destroyed by lack of oxygen or some substance (or substances) essential for the conversion of glucose to lactate is (or are) built up anaerobically in diaphragm muscle and is (or are) used up very rapidly under anaerobic conditions. The first, inherently unlikely, hypothesis was disposed of by showing that, after admission of oxygen after 15 minutes' anaerobiosis, all the synthetic and oxidative reactions of glucose function almost normally in the rat diaphragm though aerobic lactic-acid production may be reduced up to a maximum of about 30% (Table IX).

TABLE IX.—*Influence of First Incubating Rat-diaphragm Muscle Under Anaerobic Conditions on the Aerobic Metabolism of Glucose and on Oxygen Consumption**

	6 Experiments		14 Experiments	
	Controls, 60 min. in O_2	Pre-incubated in N_2 for 5 min., 60 min. in O_2	Controls, 60 min. in O_2	Pre-incubated N_2 for 15 min., 60 min. in O_2
Lactic acid ..	49·4±3·2	44·6±5·6	32·5±2·0	20·2±2·0
CO_2	7·5±0·6	6·1±0·7	5·6±0·3	4·6±0·5
Glycogen and oligosaccharides ..	2·7±0·4	3·1±0·8	1·4±0·2	1·2±0·2
Maltose	2·1±0·2	2·3±0·3	1·0±0·1	0·9±0·1
Glucose	13·8±0·8	14·3±1·1	20·8±1·1	19·8±0·7
O_2 uptake (μl.) ..	76·1±3·2	73·8±1·4	83·0±3·8	73·0±3·8

* Results expressed as μg. of glucose converted and μl. of O_2 consumed by 50 mg. of diaphragm muscle (wet weight) incubated in 0·6 ml. of phosphate buffered medium at *p*H 6·8, at 37° C., glucose concentration 0·1%. Mean values given ±S.E.M. (After Beloff-Chain *et al.*, 1959a.)

TABLE VII.—*Aerobic and Anaerobic Glucose Metabolism in Diaphragm Muscle of Rat**

Medium:	Phosphate		Bicarbonate			
Time of incubation	60 min.		15 min.		60 min.	
No. of rats	11		15		7	
,, ,, pieces of diaphragm	17		15		7	
Conditions of incubation:	Aerobic	Anaerobic	Aerobic	Anaerobic	Aerobic	Anaerobic
Lactic acid	41·3±4·5	21·0±4·1	21·8±1·3	10·2±1·2	44·5±3·3	16·7±2·2
Glycogen, oligosaccharides, maltose ..	4·6±0·4	Traces	4·2±0·3	Traces	13·7±1·3	Traces
Glucose	15·4±0·5	26·4±1·2	11·8±0·9	18·9±1·0	16·0±2·2	32·1±1·6

* Results expressed as μg. of glucose converted per 50 mg. of tissue incubated in 0·6 ml. of phosphate or bicarbonate medium. Glucose concentration 0·1%. Vessel gassed with appropriate gas for 5 minutes. Mean values given ±S.E.M. (After Beloff-Chain *et al.*, 1959a.)

TABLE VIII.—*Influence of First Incubating Diaphragm Muscle of the Rat Under Aerobic Conditions on the Anaerobic Formation of Lactic Acid from Glucose, and on Glucose Uptake from the Medium*

Experiment No.	Conditions of Incubation	No. of Rats	No. of Pieces of Diaphragm	Medium	Lactic Acid	Glucose Uptake
1	↓O_2 15 min. ↓O_2 15 ,, N_2 10 min.	6	6	Bicarbonate	14·3±1·4 37·4±8·3	52·6±1·5 64·2±5·7
	↓O_2 15 ,, ↓O_2 15 ,, N_2 10 ,,			Phosphate	14·1±2·1 61·4±6·8	35·9±1·7 76 1±6·6
2	↓O_2 15 min. ↓O_2 15 ,, N_2 10 ,, O_2 15 ,, ↓N_2 15 ,,	8	8	Bicarbonate	23·0±1·4 67·6±5·4 8·1±1·3	
3	↓O_2 15 min. N_2 10 min. O_2 15 min. ↓N_2 15 ,,*	4	8	Bicarbonate	57·1±2·4 6·9±0·6	
4	↓O_2 23 ,, ↓O_2 3 ,, N_2 15 ,,	2	2	Phosphate	35·4 87·8	
5	↓O_2 15 ,, ↓O_2 15 ,, N_2 5 min.†	4	8	Bicarbonate	24·7±2·9 52·1±7·5	

* Inert glucose added before the aerobic phase of incubation and glucose-G-^{14}C before the anaerobic phase.
† In these experiments N_2 was passed for 5 minutes and there was no further incubation in N_2.
Results expressed as μg. of glucose converted to lactic acid per 50 mg. of diaphragm muscle (wet weight) incubated in a bicarbonate or phosphate buffered medium. Mean values given ±S.E.M. Vessels gassed for 5 minutes with the appropriate gas then incubated for periods as indicated below. ↓ Indicates when ^{14}C-glucose added, following equilibration period with appropriate gas. (After Beloff-Chain *et al.*, 1959a.)

Thus the second explanation remains—that is, the aerobic formation of some product involved in glucose metabolism which is used up anaerobically.

The sum total of glycogen plus oligosaccharides formed from glucose in rat diaphragm after five minutes' aerobic incubation is still much too small to account for the quantity of lactic acid formed on subsequent anaerobiosis. This suggests that the substance (or substances) concerned has a catalytic nature. Work on its identification is in progress.

As there is no insulin effect on lactic-acid formation under aerobic conditions it could be expected that the anaerobic formation of lactic acid could also not be influenced by insulin. This is, in fact, borne out by the experimental evidence, and excludes the hypothesis that insulin acts by accelerating the hexokinase reaction.

Energy-Level Theory of the Mode of Action of Insulin

It is fundamental that any theory on the mode of action of insulin must take into account the basic fact that all reactions stimulated by insulin are of energy-requiring synthetic nature, such as glycogen synthesis from glucose and protein synthesis from amino-acids in muscle, fat synthesis in the lactating mammary gland, and both glycogen and fat synthesis in the brown adipose tissue. These endergonic reactions derive their energy from oxidative processes. It has been previously suggested (Chain, Beloff-Chain, and Pocchiari, 1956) that insulin acts by raising the energy level in susceptible cells. They now consider that, at least in part, this may be achieved by making the TPN–TPNH (triphosphopyridine nucleotide, oxidized or reduced form respectively) system more effective for synthesis.

The TPN–TPNH system is known to be required for fat synthesis (Langdon, 1955, 1957). This system is also involved in the first two steps of the oxidative pathway of glucose metabolism, the so-called pentose shunt—that is, the oxidation of glucose-6-phosphate to phosphogluconate and the oxidative decarboxylation of phosphogluconate to ribulose phosphate and CO_2. The pentose pathway of glucose oxidation occurs in different tissues to a different extent (Glock and McLean, 1954; Bloom and Stetten, 1955, and Dickens, 1956); and is particularly high in the lactating mammary gland (Abraham, Hirsch, and Chaikoff, 1954) in which a strong insulin effect on the synthesis of fat from acetate in the presence of glucose has been observed (Balmain and Folley, 1951). Abraham, Cady, and Chaikoff (1957), using glucose-1-^{14}C and glucose-6-^{14}C, have shown that in this tissue insulin strongly increases the production of CO_2 from glucose 1-^{14}C (Table X), a finding which suggests that it has shifted glucose oxidation towards the pentose phosphate pathway. A similar result was obtained by Winegrad and Renold (1958) in epididymal adipose tissue (Table XI) in which insulin has been shown to exert a strong accelerating effect on both fat and glycogen synthesis, an effect which was also observed in brown adipose tissue (Beloff-Chain *et al.*, 1956a). From these observations it is quite clear that the TPN–TPNH system is affected by insulin. In view of the fact that fat synthesis and glycogen synthesis are interdependent (Tuerkischer and Wertheimer, 1942; Wertheimer, 1945), it is very probable that the TPN–TPNH system is concerned with both syntheses, and studies to establish its exact function in glycogen synthesis are at present in progress in our laboratories.

It should be remembered that the hexosemonophosphate pathway of glucose metabolism which has been shown to be under hormonal control (Glock and McLean, 1955) provides an oxidative mechanism for drawing glucose into the cell and for making available, through the action of the aldolase–ketolase system, an extra supply of hexose phosphates (Fig. 11) which are available for glycogen synthesis provided that the appropriate oxidative phosphorylation processes, possibly TPN-linked, are functioning.

According to this theory there should be in the isolated diaphragm of the rat an increased formation of glucose-1-phosphate and glucose-6-phosphate from glucose in the presence of insulin, but the intermediates of the glycolytic cycle should not be influenced. This is in fact in exact agreement with the finding of Shaw and Stadie (1957), who showed that in the isolated rat diaphragm the formation of glucose-6-phosphate and glucose-1-phosphate is strongly stimulated by insulin

TABLE X.—*Conversion of Variously Labelled ^{14}C-glucose to $^{14}CO_2$ and Fatty Acids-^{14}C by Mammary Gland Slices**

Percentage of Added ^{14}C Recovered as $^{14}CO_2$				Percentage of Added ^{14}C Recovered as Fatty Acids			
Glucose-1-^{14}C		Glucose-6-^{14}C		Glucose-1-^{14}C		Glucose-6-^{14}C	
Insulin		Insulin		Insulin		Insulin	
−	+	−	+	−	+	−	+
19·7	35·6	2·8	1·9	4·9	9·6	10·1	23·3

* 500 mg. of slices of mammary gland prepared from lactating rats were incubated in 5 ml. of Krebs–Henseleit bicarbonate buffer *p*H 7·3, containing 50 μmols of labelled glucose. 1 unit of glucagon-free insulin was added per vessel. Gas phase, 95% O_2, 5% CO_2. Incubation for 3 hours at 37° C. Mean values of 15 experiments given. (After Abraham, Cady, and Chaikoff, 1957.)

TABLE XI.—*Effects of Insulin Added In Vitro on the Metabolism of Glucose-1-^{14}C and Glucose-6-^{14}C by Adipose Tissue of Rat.** (*After Winegrad and Renold*, 1958)

Animal No.	Oxidation of Glucose Carbon to CO_2		Incorporation of Glucose Carbon into Lipid	
	Control	+Insulin	Control	+Insulin
	Glucose-1-^{14}C in All Flasks			
101	0·57	4·06	0·19	2·25
102	0·50	3·72	0·20	1·41
103	0·36	4·87	0·20	2·96
128	0·71	3·92	0·26	1·49
129	0·68	4·69	0·24	2·32
130	0·72	4·01	0·39	1·78
Mean	0·59	4·21	0·25	2·04
	Glucose-6-^{14}C in All Flasks			
113	0·17	0·27	0·47	3·82
114	0·13	0·25	0·38	5·31
115	0·20	0·24	0·41	2·97
131	0·14	0·26	0·31	3·55
133	0·25	0·33	0·69	5·57
Mean	0·18	0·27	0·45	4·24

* All values expressed as μmols of glucose carbon-1 or carbon-6 per mg. of tissue nitrogen. Incubation carried out for 3 hours in Krebs bicarbonate buffer containing 20 mmols per litre of glucose. Lipid refers to ether-soluble lipids. Insulin concentration, when present, 0·1 unit per ml. Tissues paired so as to observe the effects of insulin in tissue from the same animal.

TABLE XII.—*Incorporation by Normal Rat Diaphragm In Vitro of Glucose-U-^{14}C into Glucose-6-phosphate and Glucose-1-phosphate**

Glucose-6-phosphate		Glucose-1-phosphate	
Insulin		Insulin	
0	+	0	+
0·11 ± 0·02	0·30 ± 0·12	1·18 ± 0·96	4·02 ± 1·07

* Results expressed as μmols per g. per 2 hours of glucose-6-phosphate and glucose-1-phosphate from glucose-U-^{14}C. Mean values of 7 and 8 experiments respectively ± S.E.M. (After Shaw and Stadie, 1957.)

inside the cell (Table XII), but that the formation of fructose-1:6-diphosphate of an intermediate phosphate ester of the glycolytic Embden–Meyerhof pathway occurring on the exterior of the cells and accounting for the major portion of lactic-acid formation is not influenced by insulin, though this compound, when added to the incubation medium, became as strongly ^{14}C-labelled as was the added glucose (Table XIII).

TABLE XIII.—*Conversion by Rat Diaphragm In Vitro of Glucose-U-^{14}C to Fructose-1-6-diphosphate; Non-labelled Fructose-1-6-diphosphate also in Medium (after Shaw and Stadie, 1957)*

	c.p.m. per Glucose Equivalent	
	Insulin	
	0	+
F–1, 6–P from medium (re-isolated after 2 hours' equilibration) ..	10,200	10,600
F–1, 6–P from diaphragm ..	0	0
Medium glucose	10,600	10,600

Fate of Glucose and Fructose in Brain Tissue

(Beloff-Chain et al., 1955b, 1955c)

I should like to conclude this report on our recent studies on carbohydrate metabolism with a short account of some results pertaining to the metabolism of sugars in brain and pituitary tissue.

Some years ago we showed, using ^{14}C-labelled glucose, that glucose in brain-cortex tissue was converted to a number of amino-acids; glutamic acid, aspartic acid, γ-aminobutyric acid, and alanine were identified (Fig. 12). The presence of free amino-acids in brain tissue has been known for some time, but it was not known that some of them derived from glucose. The question arose of the origin of the nitrogen for the transformation of glucose into amino-acids, a process which was shown to be strictly aerobic and which obviously involved transamination reactions.

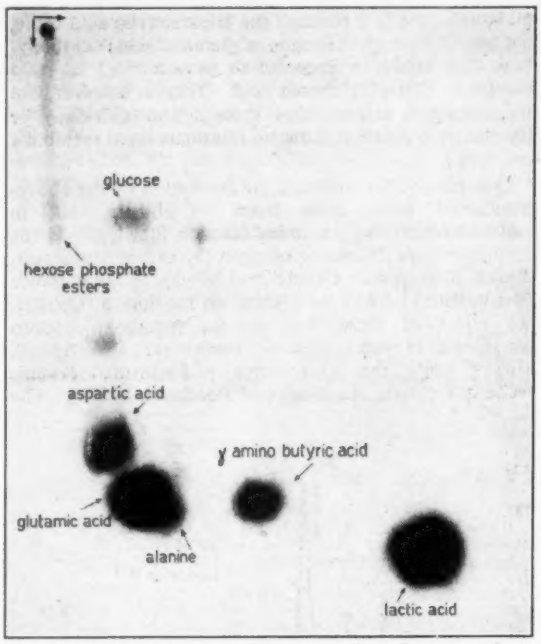

FIG. 12.—Radiochromatogram of aqueous-alcoholic extract of rat brain incubated with ^{14}C-labelled glucose. (Two-dimensional chromatogram: →butanol : acetic acid : water; ↓picric acid : tertiary butyl alcohol : water.) (Beloff-Chain *et al.*, 1955c.)

By incubating brain tissue with ^{15}N-labelled ammonium substrate (Chain, Chiozzotto, Pocchiari, Rossi, and Sandman, 1959a) it could be shown that the source of nitrogen for the transformation of glucose into amino-acids was the ammonium ion. By isolating the amino-acids from a Stein–Moore column their specific activity with regard to ^{15}N and ^{14}C content could be found by determining (1) their total amount by means of the ninhydrin reaction, (2) their radioactivity, and (3) their ^{15}N content after Kjeldahlization by mass spectrophotometry. From Fig. 13 it is evident that the areas of radioactivity and ninhydrin reaction completely coincide in the case of glutamate, aspartate, γ-aminobutyrate, and alanine fractions, whereas glycine and glutamine were only very weakly radioactive.

Mass spectrophotometric determinations of the ^{15}N content of the amino-acid fractions showed that after all the newly formed amino-acids were ^{15}N-labelled, glutamine having the highest ^{15}N content in both the amino and the amido group, the ratio ^{15}N amido nitrogen to ^{14}C being nearly 2 (Fig. 14).

It is evident from these results that glutamine is the first intermediate in the metabolic pathway of the ammonium ion and that the latter is transferred via the amido nitrogen of glutamine. An unexpected result which came to light from these isotope distribution studies was that in alanine and γ-aminobutyric acid the ratio of ^{15}N to ^{14}C was very low

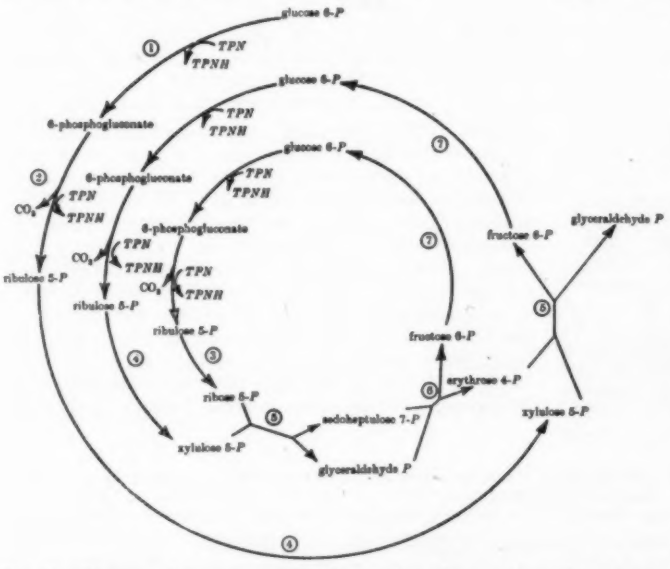

FIG. 11.—Diagram of the pentose phosphate cycle. The overall reaction for one turn of the cycle is: 3-glucose 6-phosphate + 6 TPN+ → $3CO_2$ + 6 TPNH + glyceraldehyde 3-phosphate + 2-glucose 6-phosphate. [Key to enzymes: (1) Glucose 6-phosphate dehydrogenase and lactonase. (2) 6-phosphogluconate dehydrogenase. (3) Pentose phosphate isomerase. (4) Phosphoketopentose epimerase. (5) Transketolase. (6) Transaldolase. (7) Phosphoglucose isomerase.] After Glock and McLean (1958).

(Fig. 14). If both these amino-acids originated from glutamate, the first through the tricarboxylic acid cycle, the second through the action of glutamic acid decarboxylase, they could be expected to have a $^{15}N/^{14}C$ ratio similar to that of glutamic acid. This is, however, not the case, and suggests that these amino-acids may be formed by a different, hitherto not understood metabolic pathway.

Quastel (1959) confirmed the formation of the above-mentioned amino-acids from ^{14}C-glucose, but in addition found the glutamine fraction labelled. As the only important difference between the experimental conditions employed by Quastel and by us was the presence of potassium ions in the incubation medium of Quastel, the effect of these ions on the metabolic pattern of glucose in slices of brain cortex was investigated, always using the quantitative radiochromatographic technique (Chain, Larsson, and Pocchiari, 1959b). The results, given in Table XIV, show that the presence of 0.027 M potassium ions stimulated over fourfold the synthesis of glutamine from glucose, and about doubled that of γ-aminobutyric acid, whereas the formation of glutamate, aspartate, and alanine was not significantly affected.

The oxygen uptake and the production of radioactive CO_2 were also higher in the presence of K ions (Table XIV), an effect already noticed by Quastel.

The pattern of fructose metabolism in brain is the same as that of glucose, but fructose is used to a much lesser extent by this tissue than glucose.

In Table XV a quantitative comparison of glucose and fructose metabolism is given, from which it is evident that the formation of amino-acids from fructose is nearly three times lower than that from glucose, the formation of lactate five times lower, and the production of CO_2 about one-half.

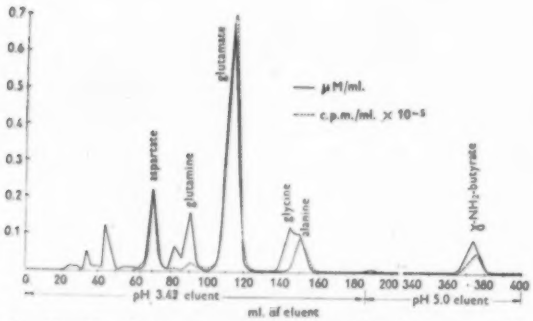

FIG. 13.—The elution curve of an extract of brain cortex of the rat incubated with glucose-G^{14}C (Chain *et al.*, 1959a).

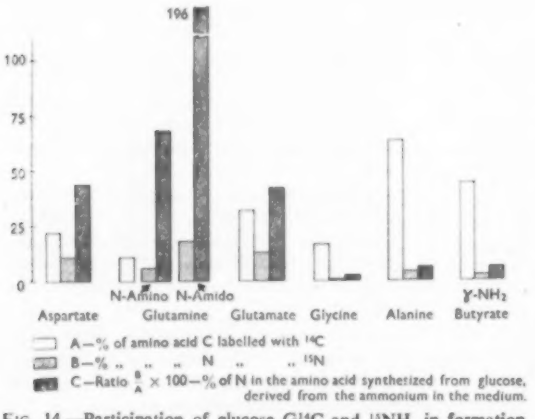

FIG. 14.—Participation of glucose G^{14}C and $^{15}NH_4$ in formation of amino-acids, by brain cortex of the rat (Chain *et al.*, 1959a).

TABLE XV.—*Metabolism of Glucose and Fructose in Slices of Rat Brain**

Metabolites Formed from Substrates	Substrates	
	Glucose (6)	Fructose (4)
CO_2	55·1 ± 3·8	26·5 ± 2·1
Lactic acid	170·2 ± 19·5	29·6 ± 1·6
Alanine	3·9 ± 0·3	1·7 ± 0·1
Aspartic acid	6·6 ± 0·3	3·8 ± 0·7
Glutamic	23·9 ± 1·9	9·0 ± 0·5
γ-Aminobutyric acid	7·8 ± 0·6	1·3 ± 0·1

* Results expressed as μg. of substrate converted per 50 mg. of tissue (wet weight) after 60 min. in 0·6 ml. of phosphate buffered medium *p*H 6·8 in O_2. Substrate concentration 0·1%. Glucose and fructose generally labelled with ^{14}C. 10 μC of radioactive substrate per vessel. Mean values given ±S.E.M. Number of experiments given in parentheses. (After Beloff-Chain *et al.*, 1955b, 1955c.)

Fate of Glucose in the Rat Pituitary

(Beloff-Chain et al., 1959b)

In the isolated pituitary gland of the rat glucose is also transformed in free amino-acids; alanine, aspartic acid, glutamic acid and a small quantity of proline were identified, while γ-aminobutyrate was absent (Fig. 15).

Apart from the free amino-acid, radioactivity appeared also in the protein fraction; on hydrolysis of the latter, aspartic acid, glutamic acid, alanine, serine, and proline were identified (Fig. 16). The active protein synthesis from glucose in the pituitary is perhaps connected with the production of hormones by this tissue. In contradistinction to brain tissue, the pituitary formed glycogen and oligosaccharides from glucose. A quantitative comparison of glucose metabolism of the pituitary gland and brain tissue, using the automatic quantitative chromatographic technique, is given in Table XVI. It will be seen that the total utilization of glucose in brain tissue is about twice as high as in

TABLE XIV.—*Effect of Potassium and Sodium Ions on Glucose Metabolism and on Oxygen Consumption by Slices of Cortex of Rabbit Brain**

	Alanine	Aspartate	Glutamate	γ-Amino-butyrate	Glutamine	Lactate	CO_2	O_2 (μl.)
Na^+ (0·04 M)	1·4 ± 0·3	0·9 ± 0·2	9·8 ± 1·8	1·31 ± 0·3	0·6 ± 0·2	93·9 ± 12·6	19·6 ± 2·2	32·1 ± 1·0
Na^+ (0·017 M) + (K^+ 0·027 M)	1·5 ± 0·4	1·3 ± 0·3	12·2 ± 3·1	2·8 ± 0·9	2·8 ± 1·0	126·2 ± 25·2	26·9 ± 2·8	41·0 ± 3·0
p	0·9	0·4	0·6	= 0·1	0·05	0·8	0·1	0·01

p considered significant < 0·1.

* The values are expressed as μg. of glucose converted and μl. of oxygen consumed per 25 mg. of tissue (wet weight). Mean values of 5 experiments given ±S.E.M. (After Chain, Larsson, and Pocchiari, 1959b.)

the pituitary; about three times as much glutamic acid is formed in brain as in pituitary, but the amount of aspartate formed is the same in both tissues and the pituitary appears to synthesize more alanine. It will be an interesting task for the future to study the physiological significance of these differences.

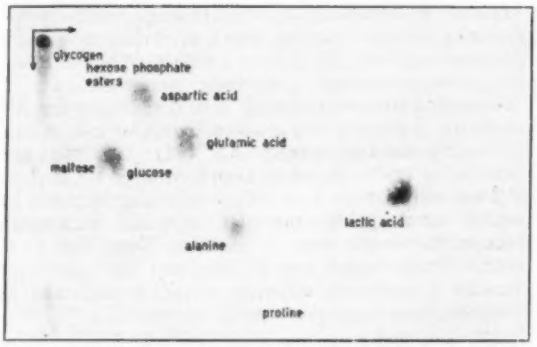

FIG. 15.—Radiochromatogram of aqueous-alcoholic extract of pituitary gland of the rat incubated with uniformly labelled ^{14}C-glucose. (Two dimensional chromatogram→sec. butyl alcohol: formic acid: water; ↓phenol: water.) (Beloff-Chain *et al.*, 1959b.)

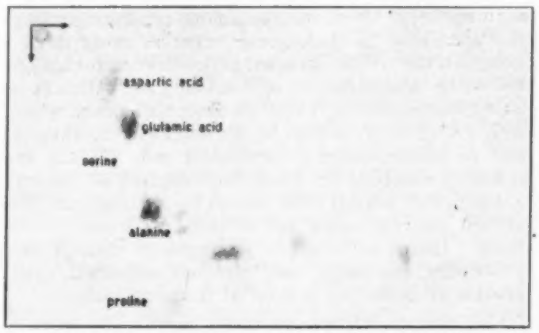

FIG. 16.—Radiochromatogram of insoluble residue after acid hydrolysis of pituitary gland of the rat incubated with ^{14}C-glucose (Beloff-Chain *et al.*, 1959b).

TABLE XVI.—*Metabolism of Glucose in the Isolated Pituitary Gland of Rat and Slices of Rat Brain**

Fraction	Pituitary Gland	Brain Slices
Alanine	6·7±0·3	3·2±0·1
Aspartic acid	4·7±1·2	4·7±0·5
Glutamic ,,	4·0±0·3	14·5±1·0
γ-Aminobutyric acid	None	4·4±0·4
Lactic acid	60·5±6·2	104·5±7·8
CO_2	16·6±2·3	58·0±7·7
Glycogen and oligosaccharides	1·0±0·1	None
Protein, amino-acids	0·9±0·2	,,
Total glucose metabolized	94·4±8·4	189·2±12·4

* Results expressed as μg. of glucose converted per 20 mg. of tissue (wet weight) after 3 hours' incubation at 37° C. in 0·4 ml. of phosphate buffered medium *p*H 6·8 in O_2. Glucose concentration, 0·1%; total radioactivity, 10 μC per vessel. Mean values of 6 experiments given ±S.E.M. (After Beloff-Chain *et al.*, 1959b.)

The findings reported in this survey represent a part of the work on intermediate carbohydrate metabolism which has been in progress in my department during the past ten years.

I hope that I have demonstrated that the new technique of automatic quantitative radiochromatography constitutes a powerful tool for studies on intermediate metabolism and opens up new avenues not readily accessible by other methods. It is of particular importance for studies conected with the elucidation of the mode of action of drugs and hormones, but should also be of interest to the clinician as a possible tool to obtain, from bioptic samples of tissues, a picture of their functional biochemical state which may eventually prove of considerable value for diagnostic purposes and complement the histological microscopical methods at present used.

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Statistics show that a great number of industrial accidents arise from such simple causes as slipping, falling, and striking against fixed objects. Each year much suffering is caused by persons falling over obstructions, tripping on stairs, or coming unintentionally into forceful contact with such things as machines, pieces of plant, stacks of materials, or parts of a building structure. Many of these accidents happen during the night or in the half-light of morning or evening, and many of them can be traced directly to the inadequacy of the artificial light provided. The latest issue of "Accidents—How They Happen and How to Prevent Them" once more draws attention to these all-too-frequent occurrences and emphasizes the importance of good lighting. Docks are among the places where accidents due to bad lighting are apt to occur, and to draw attention to the matter one exhibit in the lighting section of the Industrial Health and Safety Centre at Horseferry Road, Westminster, S.W.1, shows the striking difference between good and bad lighting at a typical dock. (H.M.S.O., No. 40, price 1s. 3d. net.)

AUTO-IMMUNE DISEASE

II. PATHOLOGY OF THE IMMUNE RESPONSE*

BY

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In the first lecture I gave an outline of a theoretical approach to immunology which I claimed had special virtues for the understanding of some immuno-pathological states. Its basic contentions were that mutation of specific immunological pattern was always taking place and that, unless there was an appropriate homoeostatic mechanism, clones of cells immunologically directed against body components would inevitably appear. Such cells undoubtedly do appear in pathological conditions, and on our current view represent the result of some breakdown of the homoeostatic mechanism. It is convenient to use the terms "forbidden clone" or "forbidden pattern" to refer to such clones and the immunological patterns they carry.

The Reality of Somatic Mutation

Some might consider that mutation is not a legitimate concept when it is applied to the somatic cells of the body. With our present ignorance of the mechanism of differentiation, it may be an unjustified extension of the concept of mutation to apply it to cell lines within the body. To establish its validity in your minds I should like to mention two recent examples where the effect of somatic mutation can be clearly seen.

The first concerns a phenomenon described by Fraser and Short (1958) in my own country which they call fleece mosaicism in sheep. Very occasionally one observes areas of long loosely crimped fleece on a sheep which should have a uniform coat of close short wool. This is an abnormality immediately visible to any sheep-owner or stockman, and when the Australian Commonwealth Scientific and Industrial Research Organization became interested in the phenomenon it was relatively easy for them to sort over by proxy about 20 million sheep, finding in the process 30 examples of mosaicism. These sheep are of particular interest from the point of view of the extent of involvement and the way the abnormal areas are distributed over the skin. In the first place, small areas of abnormal fleece are commoner than large. Of the four animals with more than 20% involvement, one had 44% and three between 20 and 25%. Fraser and Short (1958) considered that the findings were consistent with the occurrence of a specific type of somatic mutation at one of the early stages of segmentation of the fertilized ovum. When one of the cells at the two-cell stage is involved, about 50% of the fleece is long. At the next stage there will be twice as many cells in which the mutation can occur, but when it does the effect will involve only one-quarter of the skin area, and so on for further stages of segmentation. Rough calculation indicates that there is a chance of about $1:2\times10^7$ per cell generation that an early embryonic cell will undergo this type of mutation and that the frequency does not vary significantly over the early stages of the segmentation of the fertilized ovum.

It will be self-evident that a somatic mutation (or any mutation for that matter) can be recognized only when the mutating cell gives rise to an adequate and usually large number of descendants. If a mutation occurs in an adult tissue involving, say, one cell in 10^5, there will be no way in which its existence can be recognized by any simple technique.

There is, however, one interesting possibility of detecting somatic mutation which involves only a small proportion of cells. In a human individual of AB blood group there are no circulating isoagglutinins. If, therefore, a haemopoietic cell should mutate from AB to B, any B erythrocytes produced could survive as well as the genetically correct AB cells. Atwood and Scheinberg (1958) therefore examined large volumes of AB red cells for the presence of cells inagglutinable by one of the A-agglutinating plant extracts. With much labour they were able to separate from 0.01% to 0.1% of cells which had B characters and which for reasons I need not elaborate could be regarded as resulting from a genuine somatic mutation.

I believe that these two examples have the important implications (*a*) that somatic cells mutate in much the same fashion as germ cells, and (*b*) with the same order of frequency. In other words, a tremendous amount of mutation must be going on in the body. At a rough estimate, some 10^6 of the expendable replicating cells of the body may be undergoing mutation every day. I hope that this will be accepted as justification for making use of somatic mutation in discussing the aetiology of auto-immune disease. I shall be concerned almost wholly with mutation in relation to the specificity of antibody and of immunologically competent cells (I.C.C.), but it should also be pointed out that mutation of antigenic pattern as of AB→B must always be occurring and that mutant patterns could act as antigenic stimuli in the body. This is an aspect of immunology which, to my knowledge, has never been explored and which might provide an important harvest of facts and ideas.

Our present interest, however, is with the types of mutation which could result in observable consequences or which need to be postulated to account for the facts of immuno-pathology. On our hypothesis of clonal selection observable proliferation of a mutant clone could follow several types of mutation: (1) Mutation of immunological competence to a pattern corresponding to an antigen in the body; (2) development of hypermutability necessarily involving reactivity with many body antigens; (3) block in some of the transitions between different mesenchymal cell phases where this would prevent inhibitory or destructive effects of antigenic contact; (4) loss of one or more homoeostatic controls on number or concentration of cells—equivalent to premalignant or malignant change. Forestalling to some extent subsequent discussion, it is likely that all these are encountered in medicine. The first is regarded as physiological, and can result in pathological effects only when influenced by one or more of the other anomalies.

The Forbidden Clone Hypothesis

In discussing some of the auto-immune diseases, I shall make no attempt to elucidate their aetiology and pathogenesis from a consideration of the diseases themselves. Instead I shall try to elaborate the hypothesis of the forbidden clone on the basis of the clonal selection theory of immunity discussed in the first

*The second of two Croonian Lectures delivered before the Royal College of Physicians of London on June 16 and 18, 1959. Lecture I appeared in last week's issue.

lecture and to show how this hypothesis can be adjusted to the clinical and pathological findings.

To recapitulate the forbidden clone hypothesis: we assume that immunologically competent cells are unusually prone to mutation (Fig. 1), each such change giving rise to a new pattern corresponding in complementary fashion to a different antigenic determinant. In addition to maintaining a wide range of patterns of immunological reactivity, this will inevitably mean the occasional emergence of "forbidden patterns" which can react with body components. These antigenic determinants with which forbidden patterns can react may either be directly accessible as a soluble protein in one of the body fluids or as part of the surface of a circulating cell, or they may become accessible as parts of expendable cells which are in the process of autolysis or are being otherwise disposed of. In normal individuals any forbidden clone must be eliminated, or at least prevented from proliferation. As the simplest means of providing this, we assume that, at a certain stage after primary antigenic stimulation, the cell becomes hypersensitive to destruction or inhibition by contact with a small concentration of the same antigen (see Fig. 2). On this view, the failure of homoeostasis needed to allow the emergence of the forbidden clone would depend essentially on some anomaly of the processes which normally control changes of functional and morphological phase within mesenchymal cell populations.

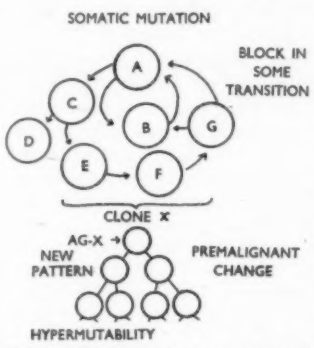

FIG. 1.—To illustrate the concept of an immunologically competent clone of mesenchymal cells and the changes that could be produced by mutation.

A.H.A.

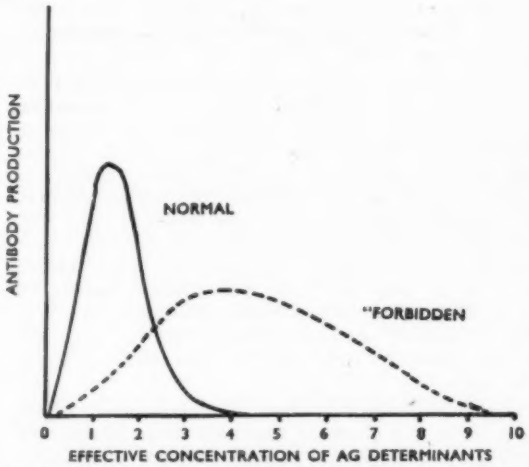

FIG. 2.—To illustrate a possible basis for the difference between a normal immunologically competent cell and an abnormal cell of a "forbidden" clone. The numerical values given for the concentration of antigenic determinants are purely hypothetical.

The anomaly might be either intrinsic to the cell as a result of somatic mutation or it could result from modification of the internal environment in which the cell finds itself. Under either of these circumstances, we can picture the emergence of clones reactive with normal body components. For them to be pathogenic, however, requires certain additional conditions.

In the first place, it is unnecessary to consider clones reactive against major plasma or body fluid components; these will be present in high enough concentration in the relevant environments to ensure the inhibition of all corresponding clones. No evidence of forbidden clones of this type appears to have been

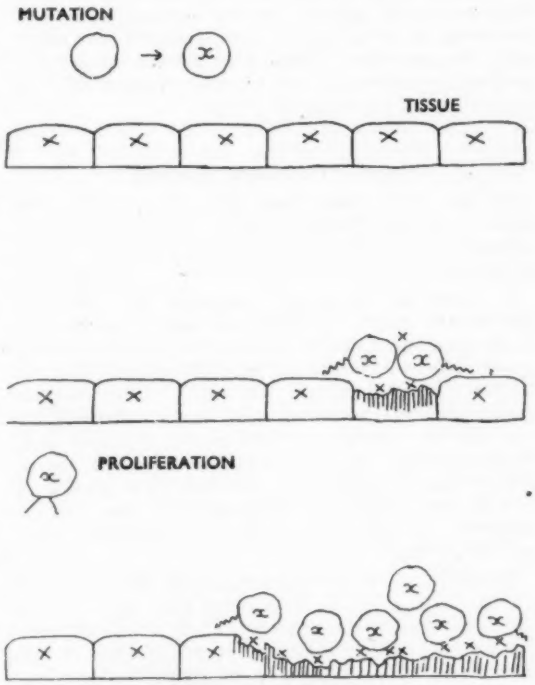

FIG. 3.—To illustrate an approach to the nature of tissue damage by cells of a forbidden clone x reacting with a normally inaccessible cellular determinant X. Contact of cell with accidentally liberated X results in damage which causes more liberation of X and hence the development of a vicious circle.

found. Similar considerations probably hold also for the more readily accessible red-cell surface components. In order that a pathogenic situation should develop from the appearance of a forbidden clone of cells reactive against antigenic determinant X, we require (*a*) that the cell can undergo primary stimulation by X, (*b*) that for one of the reasons mentioned above elimination by secondary stimulation does not occur, (*c*) that cells of the forbidden clones can react with X under conditions which will produce local damage, and (*d*) that in the course of that damage more of X is produced, so allowing the initiation of a vicious circle (Fig. 3). Where the pathogenic agent is an antibody rather than an I.C.C. the corresponding requirements to (*c*) and (*d*) are (*e*) that the I.C.C. can find a suitable niche for proliferation in the plasma cell phase, and (*f*) that the antibody can react damagingly with body cells and in the process produce or render more accessible X.

The crux of the hypothesis is that a pathological situation can only develop as part of a vicious circle. The antigenic determinant *X* must be of relatively limited accessibility if the clone is to develop at all, and if lesions are to be produced the antigenic determinant must be liberated or rendered accessible in further amount as a result of the immunological damage itself. Otherwise we should expect antibody or specifically reactive cells to be "mopped up" by what *X* was available and gradually eliminated without significant pathological manifestations.

One additional possibility must always be kept in mind—that, as in every other expendable tissue of the body, mutation can occur within the mesenchymal cells, involving other aspects of the genome than the specialized patterns that we are primarily concerned with. In particular, a clone may develop an intrinsic proliferative advantage for reasons unconnected with its immunological character.

Acquired Haemolytic Anaemia

We may now discuss two important diseases from the point of view of this hypothesis. These are acquired haemolytic anaemia and disseminated lupus erythematosus.

In acquired haemolytic anaemia the antigenic determinant usually involved is not one of the standard blood group antigens. It is stated by Dacie (1954) to be common to all human red cells except those of the very rare Rh group, –D–/–D–. The antigenic determinant has not been more closely characterized than this, and we can therefore refer to it simply as *X*. Since a Coombs test is regularly positive, we can be certain that antibody (often incomplete) is present as well as immunologically competent cells, and that the antibody can unite with *X*, which is available on the red-cell surface.

On the principle we have adopted, the effect of anti-*X* on the red cells will be to facilitate their destruction in the spleen and in the process liberate *X* in sufficiently increased amount to stimulate the proliferation of cells of clone *x*. The possibility of acquired haemolytic anaemia without circulating antibody is raised by the report of a case in a child with agammaglobulinaemia and with a negative direct and indirect Coombs test. In this case the spleen was said to show abnormally active erythrophagocytosis, raising the interesting possibility that immunologically competent cells can take on phagocytic activities. However, there seems to be no satisfactory evidence for this in normal individuals.

There are two problems of chronic acquired haemolytic anaemia that are of special interest: (1) Why are the antigens concerned obscure ones which are not those of the ABO or other easily demonstrated systems? (2) Why is splenectomy usually successful in curing or alleviating symptoms?

Some light may be thrown on both questions from Taliaferro's work on antibody response to sheep red cells in normal and splenectomized rabbits. The important feature is that, although splenectomy greatly reduces the antibody response to a single injection, the opposite effect is shown when a prolonged series of injections is given. It seems that the spleen has a special ability to accumulate antigen in sufficient amount to inhibit the production of a typical antibody against foreign cells.

This may have two implications: (1) antigen can be accumulated in the spleen from phagocyted red cells in such a fashion that it can inhibit any forbidden clones against common antigens. Only with the "less antigenic" surface antigens is there any possibility of forbidden clones flourishing. (2) For the same reason only in the spleen will there be a sufficient amount of the rarer antigenic determinant *X* for it to act as a proliferative stimulus. The spleen, too, is a rich source of all types of lymphoid cells and contains suitable environments for the development of plasma cells.

To recapitulate, for the production of forbidden clones we need, in addition to the primary immunological mutation, (1) an accessible source of the antigenic determinant in adequate amount to act as a stimulant to proliferation but not in high enough concentration to inhibit; (2) an intrinsic (mutational) or environmental modification of the competent cells widening the normally narrow gap between proliferative and inhibitory concentrations of antigenic determinant; and (3) an adequate supply of mesenchymal cells where the antigenic determinant is present in significant quantities and the conditions are appropriate for their proliferation and conversion to plasma cells.

The only suggestions that have been made in regard to predisposing factors to acute haemolytic anaemia concern infections. There are on record a number of instances of the disease following nondescript febrile infections and appearing in the course of atypical pneumonia (associated with high cold agglutinin titres) or infectious mononucleosis. Most infections, and especially these two, have a stimulating effect on the lymphoid cells, and this may on occasion be sufficient to press a mutant clone to initiate a vicious circle of the type we have described. More subtle processes, however, may well be concerned.

Disseminated Lupus Erythematosus and the Other Collagen Diseases

The collagen diseases as exemplified by disseminated lupus erythematosus (D.L.E.) present a much more complex situation. Again we shall adopt the approach of presenting an interpretation based on the forbidden clone hypothesis and seeing how this agrees with the clinical facts rather than attempting to deduce the nature of the aetiological factors from a consideration of the disease itself.

D.L.E., then, is regarded as a condition resulting from the proliferation and pathogenic action of forbidden clones directed against a variety of antigenic determinants whose only common feature is that they are liberated as a result of tissue reaction to immunological damage. Of the almost infinite number of antigenic determinants which might fit into this requirement, the proportion active at any given time and in any given patient will vary with circumstances. This is in line with the extraordinary range and variability of symptoms in these conditions. D.L.E. is characteristically multiple in its symptomatology, and grades, virtually imperceptible, into other collagen diseases.

Fig. 4 is designed to show the interrelations of the diseases in this group to rheumatic fever, rheumatoid arthritis, and the typical collagen diseases. It has been compiled from statements in the literature in regard either to cases where there was difficulty in deciding between two or more diagnoses, or where there was clear

evidence that the condition changed from one to another, justifying a different diagnosis. A point of particular interest is the frequency with which one or other of the "malignant" forms of collagen disease may arise from what is initially diagnosable as rheumatic fever or rheumatoid arthritis. In the great majority of cases these conditions do not, of course, go on to the malignant form. The nature of the interrelationships amongst the auto-immune diseases will obviously become clear only when we can define the antigenic determinants which are involved in the various conditions. For the present we are limited to rather meagre hints from clinical pathology.

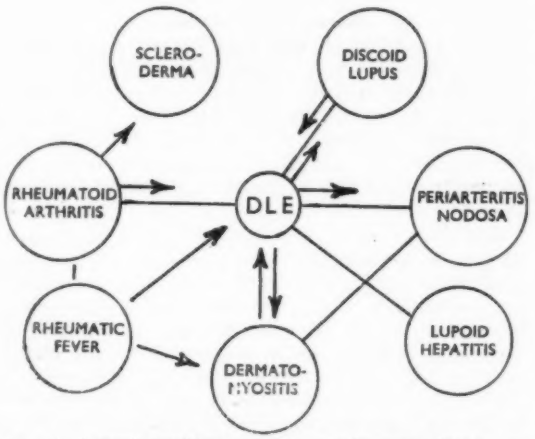

FIG. 4.—Interrelationships amongst auto-immune diseases as suggested by statements in the literature of apparent conversion of one form into another or of difficulties in differential diagnosis.

Hints from Clinical Pathology

The first possibility is an antigenic determinant which makes its appearance when the γ-globulin of an antibody becomes partly denatured on combining with its corresponding antigen. The possibility of this has been stressed by Najjar and Fisher (1955) and Milgrom *et al.* (1956). Obviously the appearance of this antigen must be a common occurrence, and on general grounds one would expect that the body would be immunologically non-responsive, subject to elimination of the corresponding clones. The findings of Milgrom *et al.*, however, indicate that quite a significant small proportion, around 1%, of apparently normal persons do have circulating antibody of this type. There is much to suggest that deposits of γ-globulin shown by fluorescent antibody staining methods in the glomeruli of the kidney and other situations in D.L.E. and related diseases represent the deposition on denatured γ-globulin of the corresponding antibody, which in its turn adds to the deposit by now becoming the antigen. Apart from playing a part in the gradual deterioration of kidney function, this antibody seems to be of relatively little direct importance. It remains to be determined, however, whether immunologically component cells of this specificity may not be concerned in helping to produce damage in areas subject to inflammatory processes.

The characteristic serological change in rheumatoid arthritis is the presence of an abnormally large globulin molecule in the circulation. In the opinion of Franklin *et al.* (1957), this represents a complex of about six normal globulin molecules with a large normal globulin (S_{18}), the union being perhaps immunological in character. The possibility that immunologically competent cells of denatured globulin specificity are responsible for the damage in articular and periarticular areas does not seem to have been excluded. On general grounds, however, it would seem that some other substance, presumably a common product of cellular damage, is the carrier of the significant antigenic determinants that are concerned in acute arthritic manifestations.

The second region of significance is in regard to nuclear components and, in particular, to the L.E. cell factor. Findings by various authors are consistent that in D.L.E. sera there are reactive globulins which correspond to antigenic determinants present in mesenchymal cell nuclei. According to Franklin *et al.*, there are a number of different antibodies or reactive globulins of this character, one or more of which are responsible for the L.E. cell phenomenon. Included in this complex are antibodies against purified deoxyribonucleic acid (D.N.A.). It is noteworthy that these globulins are not species-specific, the antibody against D.N.A. being, for example, equally active against D.N.A. from human thymus, calf thymus, pneumococcal transforming principle, and T2 bacteriophage.

The clue to these forbidden antibodies is almost certainly to be found in the lymph nodes, which in D.L.E. are usually enlarged and contain focal areas of necrosis characterized by gross pyknosis and fragmentation of nuclei. The forbidden clone hypothesis would describe the situation as follows: In every lymph node there can be seen damaged pyknotic lymphocytes, often undergoing phagocytosis. Potential antigenic determinants of nuclear origin must be constantly available and, in the normal individual, prevented from immunological activity by the standard homoeostatic machinery. Under the postulated ineffectiveness of that mechanism immunologically competent cells with any of the forbidden patterns will be enabled to proliferate. Cells of such clones now moving around the body will be apt to lodge in any regions where the relevant antigenic determinants are being liberated from damaged cells. In an otherwise healthy individual there may be virtually nowhere else than in the lymphoid tissue, and here we might well find a secondary homoeostatic mechanism coming into action by the gross accumulation of antigenic determinants in the lymphoid tissues.

But with the occurrence of some minor damaging process—for example, extensive sunburn, development of hypersensitivity to penicillin, serum sickness, viral hepatitis—a focus is provided to which the pathological forbidden clones of lymphocytes and other mesenchymal cells can flock. There the damage will be accentuated by the interaction of antigen with immunologically competent cells, possibly with destruction and partial autolysis of the immunologically competent cells. (This is a probable origin of the haemotoxylin bodies.) As the process develops, both immunologically competent cells and antibodies will increase in amount and diversity, since there are undoubtedly hundreds of different antigenic determinants against which forbidden clones of cells can be developed, and which can be liberated from damaged cells of various types.

The essential feature of this hypothesis, as of the clinical picture of the severe collagen diseases, is the

extreme variability in extent and distribution of the pathological process among different organs. The whole hypothesis calls for the play of accident in determining which mutant clones will be "chosen" by the availability of antigenic determinants in the relevant lymphoid tissues at appropriate concentrations. The diseases are rare enough to suggest that somatic mutations (other than immunological) in mesenchymal cells are probably necessary for the conditions to develop. One such mutation which has already been suggested is to an insusceptibility to the inhibitory action of secondary antigenic contact. Apart from these, one could probably postulate that sooner or later all the immunological patterns would arise by immunological mutation. The variability would arise (*a*) by the extent to which clones were stimulated to proliferate; (*b*) by the degree to which plasma cell development occurred, and, on the other hand, (*c*) by the extent to which opportunity was available for interaction with antigenic determinants in regions not directly associated with immunological productivity; and (*d*) by the strength of controlling factors, especially steroid hormones.

Hints from Clinical Data

Some interesting hints may be derived from the clinical data. There is, for instance, well-authenticated information that dermatomyositis is associated with malignant disease to a significant degree. On our present approach this suggests that a spreading malignant growth will be associated with the local liberation of various cellular antigens, including in many instances antigenic determinants, especially characteristic of muscle tissue. The other predisposing conditions would have to be present, but the direction in which the build-up of proliferating forbidden clones would occur might well be determined in this fashion. A point arising from this suggestion is the indication that immunologically competent cells making contact with antigenic determinants at a local site could proliferate at a distant site—for example, spleen or thymus—provided the appropriate immunological conditions were fulfilled.

Periarteritis nodosa is probably the most difficult of all the conditions to interpret, although the characteristic lesions are to be seen to some extent in all the "collagen diseases." A clue may be found in the sex incidence—unlike the other conditions, this is more frequent in men than in women—and in the fact that it is to some extent correlated with hypertension. As in the other conditions, it appears that damage by some other process renders a tissue vulnerable to the vicious-circle effect of immune damage.

Another point of special interest is that the lesion in the Arthus reaction in the rabbit appears to be of very similar character to periarteritis nodosa. Rich and Gregory (1943) have also found that in rabbits given large doses of foreign protein vascular lesions of the same type occur, and, further, that in patients dying after having suffered severe serum sickness very similar lesions occurred. In all these conditions antigen–antibody precipitation in the tissues is a possibility, and it is usually considered that this gives rise to endothelial damage, the other changes being secondary to this.

If periarteritis nodosa is an auto-immune disease in most instances, the lesion will need to be interpreted as a vicious circle of some sort. It could be supposed that an endothelial lesion of any origin could render accessible cytoplasmic or nuclear components with which antibody or immunologically competent cells could react damagingly and so give rise to further liberation of accessible antigenic determinant. As in all these conditions, the precise antigenic determinants involved are unknown. They might be the same as those involved in quite different types of lesion or they may be specific to an antigen present only in vascular tissues. It is of special interest that periarteritis nodosa may be localized to particular organs, notably gall-bladder and appendix Throughout the indication is strong that two things are required; an initial vascular lesion and an immunological anomaly that allows the development of a vicious circle leading to spread of the lesion.

Questions to be Answered

If this outline of the "malignant" auto-immune diseases is correct, there are several outstanding questions to be answered: (1) What are the antigenic determinants concerned? (2) What is the anomaly in the homoeostatic mechanism? (3) In what way do the "non-malignant" conditions, rheumatic fever and rheumatoid arthritis, differ from the "malignant" ones?

The Antigenic Determinants.—Some indications have already been given that (*a*) components of denatured γ-globulin and (*b*) more than one nuclear component are concerned in D.L.E. In addition, we know that a variety of red-cell determinants may be involved in haemolytic anaemia. The wide reactivity of certain sera in Gajdusek's auto-immune complement-fixation (A.I.C.F.) test suggested strongly that in some at least of the cases there was a plethora of anomalous forbidden patterns in the circulating antibody and hence by hypothesis in the clones concerned in their production. A point of particular interest was the failure of certain pathological sera to react with antigens prepared from the patient's own liver, although reactive against antigens from other individuals. It may be objected that the reactive globulins in such sera cannot legitimately be referred to as antibodies. This is true on the Haurowitz–Pauling theory of antibody production, but on the clonal selection theory an antibody is much less specifically definable. Any population of globulin molecules in a body fluid which can unite to a specifically limited range of chemical patterns can justifiably be called antibody on this theory.

Our view would be that in a florid case of D.L.E. with a high titre A.I.C.F. reaction a wide and variable range of reactive globulins with forbidden patterns can be present. It is specially significant that in most instances rat or rabbit tissues will serve as antigen in complement-fixation tests nearly or quite as effectively as human tissue emulsions.

The Anomaly in the Homoeostatic Mechanism.—Some suggestions have already been made about possible anomalies in the homoeostatic mechanism which would allow the emergence of forbidden clones. It is probably inappropriate to make any more detailed suggestions until more experimental evidence is available. It is to be hoped that more work will be done on hydrallazine and related compounds to see whether there is an important clue to be found here. It may be significant, however, that only 10% ± of patients on hydrallazine have ever developed frank signs suggestive of D.L.E.

How Do "Non-malignant" Conditions Differ from "Malignant" Ones? — Elsewhere, suggestions have been made that rheumatic fever is a manifestation of

forbidden clones of cells arising in the lymphoid tissue of the pharyngeal region. Here the homoeostatic mechanism is assumed to be broken down by the changed local conditions associated with streptococcal infection and re-established with the waning of the local infection. This is as yet no more than a working hypothesis which may stimulate experimental work toward the characterization of forbidden clones—if they exist.

Conclusion

This discussion of the auto-immune disease represents a purely theoretical study, but I believe it is important that we should have a clear theoretical background if we are to devise means to prevent or treat these conditions. One of the greatest difficulties in their study is our inability to produce analogous conditions in experimental animals. Where experimental models are not available there is perhaps greater justification for the speculative type of approach that I have used.

What I should specially like to leave with you is a sense of the existence of cellular populations within the body which, like a population of bacteria in a test-tube or rabbits in a continent, are subject to mutation, proliferation, death, and selective survival. The population dynamics of the body cells represents, I believe, the most fertile of all the broad fields of medicine that still await adequate study. Just as I completed writing these lectures, I found a new paper by Szilard (1959) putting into mathematical form a thought that has been becoming more and more insistent in my own mind — that ageing is essentially the integration of mutational damage to somatic cells. If this is true, and if I am correct in the interpretation of the pathology of immunity, and if the somatic mutational approach to cancer withstands the challenge of the virologists as I believe it will, then somatic mutation as an aetiological consideration may come to dominate the whole of medicine in so far as it is concerned with the waning half of human life.

The approach is an unpopular one—mutations are irreversible and there is no presently conceivable way in which the process can be prevented. Curative approaches, too, must be indirect and largely empirical. Medical science, however, is growing up, and I think it is time that we stopped fostering the naive expectation of the public that genetic anomalies, including feeble-mindedness, cancer, the degenerative disabilities of age, and death itself, will all eventually be overcome as surely as we can deal with pneumococcal pneumonia or malaria. There will always be much that we can do as doctors, but we must base our expectations upon facts and leave a belief in miracles to others.

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KARTAGENER'S SYNDROME WITH FIBROCYSTIC DISEASE

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Situs inversus has been recognized from antiquity; among the ancients Aristotle is said to have noticed two cases of transposed organs in animals. The Renaissance and its aftermath saw a renewed interest in anatomy; Fabricius, one of the successors of Vesalius at Padua and among whose pupils was William Harvey, described a case of reversed liver and spleen in the human in 1660; and Petrius Servius, in 1615, recorded a case of transplantation of the viscera (Lineback, 1920; Sherk, 1922). It was not until the early nineteenth century that the condition was first diagnosed clinically. By the latter part of the century such a diagnosis could be confirmed with accuracy by the newly discovered roentgen rays. Over 1,000 cases of this abnormality have now been recorded, and it has been estimated that it occurs as often as one case in approximately 1,400 of the general population (Johnson, 1949). It is not incompatible with normal health, however, and it is often related how Elisha Bartlett, a distinguished physician of his day, lived a normal life-span with complete transposition of the viscera. The condition itself may be complete or partial, when it may be limited to the abdominal or thoracic organs alone. It is often associated with numerous other congenital abnormalities (see review by Wood and Blalock, 1940).

Kartagener (1933) described a group of patients with bronchiectasis who had situs inversus, recognized in the main by the discovery of dextrocardia; his cases also had abnormalities of the paranasal sinuses. It has become general experience that the incidence of bronchiectasis and sinusitis in patients with rotational abnormalities is greater than that noticed in the general population; for instance, Adams and Churchill (1937) found that 21.7% of a series of patients with situs inversus studied by them had bronchiectasis; the comparable incidence of bronchiectasis in the general hospital population was 0.36%. In view of the association of bronchiectasis with the obvious congenital abnormalities in the situs inversus cases, the hypothesis has been advanced that this is one type of true congenital bronchiectasis, with cystic changes in the lung as a result of dissociated tissue held to be primitive foregut tissue occurring within the lung bud. It is the opinion of others, however, that the bronchiectasis is acquired from infected sinuses which are congenitally malformed. It is our purpose to record a further case of this syndrome in a patient in whom it seemed likely that the bronchiectasis and other clinical failures were associated with fibrocystic disease of the pancreas.

Case History

A man aged 20 woke on the morning of March 19, 1957, with epigastric pain. This at first came in spasms and was

likened to acute hunger. He took his breakfast and went to work complaining of a diffuse, intermittent, colicky pain, only to return home some hours later owing to a constant aching pain in the central abdomen. He felt anorexic and nauseated but did not vomit. Later in the evening the pain was felt more severely in the left iliac fossa, where it persisted until the time of operation. He had no frequency of micturition or dysuria. His bowels had moved normally earlier in the day.

On admission his temperature was 99.4° F. (37.4° C.) and his pulse rate 86. His tongue was moist but covered with a white fur, and there was marked halitosis. He was very tender in the left iliac fossa, with accompanying hyperaesthesia, and there was guarding and rebound tenderness at this site. He was noticed to have marked finger-clubbing. Chest examination revealed dullness and moist rales at the right base; the apex was palpated in the fifth right interspace 3½ in. (9 cm.) from the midsternal line, and liver dullness was present on the left side. A diagnosis of acute appendicitis with transposition of the viscera was made and appendicectomy carried out via a left iliac fossa incision. The caecum was withdrawn from the wound and the appendix was found to be tense and distended with pus at its tip, which was greenish blue in colour for ¾ in. (2 cm.). It was removed in routine fashion: abnormal rotation, the absence of the pelvic colon, and the presence of the liver on the left side of the abdomen were confirmed.

His past medical history was ascertained in detail. He was a first child of birth weight 8½ lb. (3,885 g.), whose parents were healthy; his mother's age at the time of his birth was 28 years. There was no history of chest disease in the family. He was breast-fed. From the age of 3 weeks until adolescence he was frequently in hospital because of recurring upper respiratory infections. At the age of 3 months he had a collapse of his right lung. As a child he was very susceptible to infections and failed to thrive properly. At 11½ years he was only 66% of his expected weight. At this time bronchiectasis at the left base was discovered. At 14 years a lipiodol bronchogram showed bronchiectasis of left middle and lower lobes. An *x*-ray film of his sinuses showed them to be small and underdeveloped. After this, though the possibility of surgical treatment for bronchiectasis was suggested, he did not report for further treatment until the onset of his acute appendicitis.

Special examinations were performed as follows.

Chest Screening and Bronchogram

X-ray examination of the chest showed dextrocardia and a left-sided aorta (Fig. 1); the left dome of the diaphragm was higher than the right probably owing to a left-sided liver. The gastric air bubble was present on the right side. Screening confirmed these changes, and a barium swallow revealed an indentation of the right side of the oesophagus opposite the aortic impression. The indentation was due to extrinsic pressure, probably an anomalous vessel, or possibly a double aortic arch. Bronchograms showed a bronchiectasis of the left lower lobe and lingula; only the proximal parts of the lower lobe and lingula filled, and these were obviously abnormal. Some homogeneous opacities previously noted at screening and thought to be cysts were outlined with contrast medium and shown to be dilated bronchi. The frontal sinus was underdeveloped and there was mucosal thickening in both maxillary antra. Electrocardiographic recordings showed changes typical of dextrocardia.

Investigations Relative to Mucoviscidosis

Chronic pulmonary disease in childhood or adolescence, if associated with failure to develop normally, should be investigated for the possible association with generalized fibrocystic disease or mucoviscidosis.

If pancreatic insufficiency is present the ratio of split to unsplit fat in the stool and its nitrogen content will vary from normal values, and this should indicate the lack of the appropriate enzyme, lipase or trypsin. The daily fat excretion on a mixed diet was 8.7 g. (above 5 g. is evidence of steatorrhoea). Examination of the split and unsplit fat in the stool showed that 29% was split and 71% unsplit (normally as much as 80% should be hydrolysed to fatty acids). The nitrogen present in the stool was 3.94 g./24 hours. (Wollaeger *et al.* (1947) gave 0.8—2.5 g./24 hours as the normal range.)

Darling *et al.* (1953) showed that the sweat-gland secretion in fibrocystic disease was abnormally high. In this instance the trunk of the patient was heated and sweat was obtained from the neck region, which was perspiring freely. A rapid means of detecting the sodium chloride abnormality is to employ the test plates of Shwachman and Gahm (1956), in which silver nitrate and potassium chromate are embedded in an agar medium. In patients

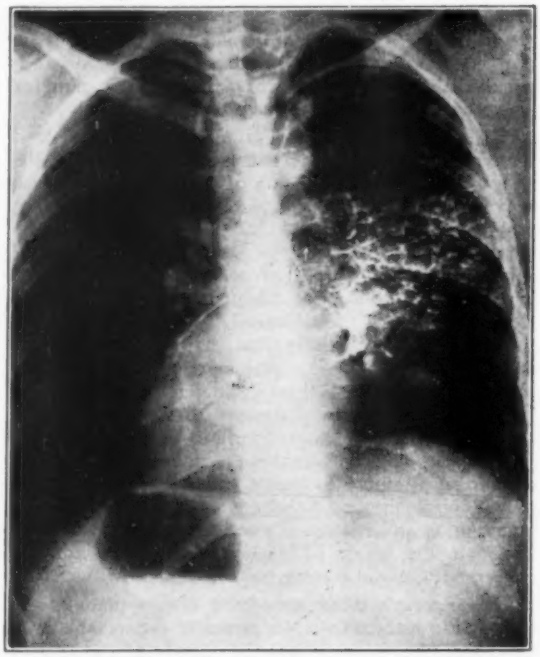

FIG. 1.—Radiograph of chest showing dextrocardia. Note gastric air bubbles on right side and slight elevation of left dome of diaphragm. Lipiodol has been given into the left bronchial tree.

with abnormally high sweat-salt content, contact of the body with the surface of the plate produces a white precipitate. Consequently the method of digital imprint is used (Fig. 2).

Analysis of the electrolyte composition of sweat from the patient showed abnormally high values for sodium chloride within the accepted range for fibrocystic disease recorded by di Sant' Agnese (1956) (see Table). Analysis of salivary electrolytes showed the same trend: sodium 20 mEq, chloride 27 mEq (as sodium chloride) per litre (normal values: sodium 8.7–23.9 mEq/l., chloride 8.4–17.7 mEq/l.).

Values (mg./l.) for NaCl in Sweat and Urine, Showing Normal Range and Range of Determinations for Patient. The Values Quoted for Sweat NaCl (di Sant' Agnese) for Fibrocystic Disease—Sweat Chloride 50–160 mEq/l. and Sodium 80–90 mEq/l.

	Sweat from Mid-abdomen		Urine 24-hour Sample		Aldosterone Excretion in Urine (μg./day)
	Chloride mEq/l.	Sodium mEq/l.	Chloride mg.	Sodium mg.	
Normal ..	8–52	15–60	4,000–7,000	2,500–4,500	0·6–2
Patient ..	135–150	155–165	1,000–1,500	500–900	2–3

A 24-hour sample of urine, on a salt intake of 5–10 g./day, gave a mean reading of 2.039 g. of sodium chloride per litre (normal range, see Table). In view of the abnormal losses of sodium chloride in the sweat it seemed possible that reduction of sodium chloride in the average daily output of urine was due to active retention of sodium chloride to prevent excessive loss. Aldosterone excretion was determined to ascertain if excess of this hormone was being secreted to help effect this compensation. The excretion amounts were raised in two determinations above the normal range (Neher and Wettstein, 1955) (see Table).

The high sweat-chloride content was confirmed by the Shwachman test when a +++ reaction was obtained (Fig. 2). This test was applied to the patient's parents and siblings. Both parents were negative, but one of the siblings showed a reaction equal in degree to that of the patient—without having any evidence of chest disease.

FIG. 2.—Shwachman test on silver-nitrate-impregnated agar plate. Upper plate is normal control. Lower plate shows imprint of finger from patient.

Miscellaneous

Examination of the oral mucosa for the presence of sex chromatin in the nuclei showed a complete absence of the destructive chromatin mass. The presumptive chromosome constitution is therefore XY. This examination was performed because of a possible link with other genetic upsets.

The blood group was O, rhesus positive, with genotype Rr (CDE/CDE). The blood picture showed: haemoglobin, 74%; reticulocytes, 1%; P.C.V., 39%; M.C.V., 70 cubic microns; M.C.H.C., 28%, with an appearance typical of iron deficiency.

Agammaglobulinaemia was excluded by a normal plasma electrophoresis pattern. This examination was performed because of a possible association with recurrent chest disease.

Discussion

Many of the cases of situs inversus recorded in the literature, remaining undiagnosed till treatment by operation, were cases of partial transposition, which is known to occur in three main forms: there may be partial transposition of both the thoracic and abdominal organs, and transposition affecting the abdominal organs alone or the dextrocardia alone. Recognition of total transposition of the viscera in this instance enabled a diagnosis to be made and treatment to be planned as though the patient were the mirror image of a more normal individual. The presence of the apex beat on the right side, liver dullness transposed to the left side, where commonly gastric resonance is found on examination, and the shadow of gas in the fundus of the stomach on the right side of the abdomen were the main criteria. Left-handedness is not present in higher incidence in patients with situs inversus, and this is an unreliable guide (Cockayne, 1937), but in cases where the diagnosis is in doubt as a result of discrepancies in the above findings a more reliable sign is the lower position of the right testicle (Cholst, 1947).

The anatomical abnormalities in situs inversus may be summarized as follows. The heart lies to the right of the midline, and its chambers are reversed, the apex being the right ventricle, from which rises the aorta. The aorta arches toward the right, giving off the innominate artery (which subsequently divides into the left common carotid artery and the subclavian artery), the right common carotid artery, and the right subclavian artery. The great veins empty into the left atrium, whence the blood passes into the left ventricle, the pulmonary arteries, the pulmonary capillary bed, the pulmonary veins, and the right atrium respectively. The thoracic duct lies to the right and empties into the right subclavian vein near its junction with the internal jugular vein. The lungs are structurally reversed, the right being bilobed and the left trilobed. Intra-abdominally, the cardia lies to the right of the midline and the lesser curvature extends toward the left. The spleen is on the right, and the gall bladder and liver (with reversal of the normal lobular arrangement of the latter) on the left. The entire intestinal tract is reversed, with the caecum and appendix on the left and the sigmoid flexure of the colon in the right iliac fossa.

The topography of abdominal pain is of interest when the alimentary tract of patients with malrotation is affected by disease. Cases such as this one tend to confirm the arguments for true visceral pain (see Brown, 1942), since the patients can be interpreted as experiencing the central abdominal pain merely as the artificial displacement of tissue from the midline. No matter how the gut has rotated or migrated to a new abdominal site, its nerve supply and sensory experiences remain that of a simple straight tube situated in the middle of the abdomen. The later sharp and more accurately localized pain of appendicitis is the result of irritation by exudate of the parietal peritoneum which has a cortico-spinal nerve supply. Although many cases of situs inversus are recorded in the literature, comparatively few in the experience of Hershman (1952) have been described with appendicitis: on the contrary, Blegen (1949) recorded 96 examples of appendicitis with transposition of the viscera, and in a proportion of his cases the pain was on the right side, although the appendix was on the left side.

The causation of situs inversus has been the subject of much doubt. In general, it has been regarded as genetically inherited, and the support for this theory has come largely from the study of the families in which this condition has been known to occur; alternatively, it has been alleged to result from some environmental upset of the fertilized ovum. Our patient was thought to have mucoviscidosis, since he had bronchiectasis, sinus infection, and anomalies of the sweat secretion and the exocrine secretion of the pancreas, consistent with this diagnosis (for review see di Sant' Agnese, 1956). Mucoviscidosis is a disease in which hereditary transmission by a recessive genetic mechanism is likely; the most acceptable hypothesis at the present time is that the disease is due to a gene or genes which cause overt disease in homozygotes and which give partial or no expression of the disorder in heterozygotes

(Childs, 1955). Whether this genetic inheritance is sufficient to provoke any inherited situs inversus as a genetic factor, or might influence the fertilized ovum as an acquired factor acting through its early environment, is a matter for speculation only. In support of the acquired theory of situs inversus is the fact that two environmentally acquired conditions—namely, agammaglobulinaemia and toxoplasmosis—have already been described in association with situs inversus (Collins and Dudley, 1955; Van Creveld *et al.*, 1948).

Since many cases of mucoviscidosis can have the latent type of disease and may pass unrecognized in the community except by the sweat-composition defect, it is possible that association between situs inversus and mucoviscidosis is more common than one at first imagines, and it might be the case that the Kartagener syndrome is a form of situs inversus associated with fibrocystic disease. The abnormality in the lungs and recurrent infection of the sinuses formerly led to the spontaneous belief that the lesions were almost certainly congenital in type, for the good reason that they occurred in the presence of such a pronounced congenital defect as situs inversus. If our case is not an exceptional one, an alternative view is now put forward—that the bronchiectasis and sinus infection may be occasionally associated with mucoviscidosis, and that, if searched for, concomitant defect such as faulty exocrine secretion of the pancreas and sweat will be found. It is supportive evidence for this theory that the defects in sweat composition were found in another member of the patient's family. Cases have been described in the literature which are capable of interpretation according to our hypothesis; for instance, Bergstrom *et al.* (1950) record two cases of the Kartagener triad, with two additional cases of bronchiectasis among six siblings. It is fairly well known that bronchiectasis arising in several members of the same family should arouse the suspicion that they have inherited some of the features of mucoviscidosis, and that examination of the sweat composition will usually not only confirm this but reveal other members of the family affected as latent cases.

Summary

A case of situs inversus viscerum is described requiring appendicectomy for acute obstructive appendicitis.

This patient with situs inversus also had had repeated attacks of pulmonary infection related to bronchiectasis and sinusitis, the syndrome described by Kartagener in 1933.

The patient had anomalies attributable to mucoviscidosis or fibrocystic disease—namely, abnormalities in sweat-gland secretion and in the content of the fat and nitrogen in the stool. He was aged 20 years—unusual in patients suffering from known mucoviscidosis. The anomaly of the salt content of the sweat was found in a sibling.

We thank Professor C. F. W. Illingworth, in whose wards the patient was treated, for helpful criticism and advice.

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PHYSIQUE AND HAZARDOUS OCCUPATIONS

A COMPARISON OF THE PHYSIQUE OF 160 ROYAL MARINES

BY

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The physique and choice of occupation of three groups of men serving in the Royal Marines have been studied. The initial object was to compare the physique of a particular branch known as swimmer-canoeists with that of branches not engaged in such severe training, but comparison of other trades also showed differences of interest.

1. *Swimmer-Canoeists* receive special training in canoeing in rivers and tidal waters, and underwater swimming for such purposes as underwater demolition and beach reconnaissance. Training is arduous and is unlikely to be survived by those who are not mentally and physically robust. Training is largely carried out at night. Underwater swimming in these conditions is a sufficiently trying experience in itself; it is the more so when it forms only one item amongst overland night marches, parachute drops, and heavy physical labour and exposure involved in canoeing. The group here presented represents the entire training staff of an establishment where swimmer-canoeists are trained; no trainees are included.

2. *General Duty Marines.*—This group consisted of a cruiser detachment of Royal Marines to whom I had access. As such they were engaged in the normal peacetime training of the Royal Marines, not so severe or exacting as that undertaken by group 1, but more arduous than that of many occupations. All were questioned about their intentions regarding volunteering in the future for more arduous training. Any having such intentions were excluded.

3. *Other Special Branches.*—A third group of men belonging to miscellaneous trades, not involving major hazard, were also studied. They comprised clerks, drivers, vehicle mechanics, and cooks. All those available to me at one given time were measured, with the exception of those relegated to their particular trade for medical reasons.

These three occupational groups might be expected to embrace gradually diminishing degrees of "somatotonia," the component of temperament described by Sheldon as correlating most closely with mesomorphy or muscularity. Somatotonia includes

such traits as liking for physical exercise, resistance to physical discomfort, and the ability to withstand physical danger and undertake hazardous activities. Thus, if the qualitative relationship between physique and temperament reported by Sheldon and Stevens (1942) is to be confirmed, it would be reasonable to expect to find a higher proportion of more muscular or mesomorphic builds among swimmer-canoeists than among other branches. This appeared to be the case.

Assessment of Physique

The method employed is that devised by Parnell (1957) and modified from his standard deviation method (Parnell, 1954).

The assessed physique is called the "phenotype" by Parnell to draw attention to the fact that it does differ importantly from Sheldon's somatotype (Sheldon and Tucker, 1940). Both are estimates of the fundamental and theoretical morphogenotype. The somatotype is a broad concept and represents the nearest approximation to it, and is based on all available evidence, including, if time permits, lifelong study. The phenotype does not claim such a fundamental nature, and is affected to some extent by the variations produced by exercise, nutrition, and disease in muscle girth and skinfold measurements, though measurements of bone are more stable.

The ages of men under study are relevant, as the muscularity "4" chart is applicable only to the age group 18–25, from which the measurements on which it is based are drawn. The ages of the groups studied are shown in Table I.

TABLE I

Group	No.	Mean	Range
1	41	24·5	21-34
2	62	21·5	18-28
3	57	22·2	18-32

Men whose ages were over 25 were questioned on their weight history, and any marked changes taken into account. This was also done where muscular hypertrophy had resulted from special exercise, such as weight-lifting. The possibility that the special training of group 1 might produce muscular hypertrophy is relevant, and is discussed later.

Results

The average measurements for the three groups are listed in Table II. The differences between the group averages are calculated and a test of significance is applied (Bradford Hill, 1955). The differences and their significance are shown in Table III.

To correct for height variation between the groups, the differences have been scaled down in the appropriate ratio and compared with the original standard error of the difference. This tends to diminish the significance of any difference. The corrected figures are given in Table IV; their significance remains unchanged.

TABLE II

	Group 1 Canoeists	Group 2 Cruiser Detachment	Group 3 Other Branches
Number	41	62	57
Age	24·5	21·5	22·2
Height (in.)	70·26	69·1	69·5
Weight (lb.)	165·6	155	152
Ponderal index	12·79	12·95	13·02
Biceps (in.)	12·45	11·80	11·65
Calf (in.)	14·25	13·80	13·65
Humerus (cm.)	7·24	6·93	7·02
Femur (cm.)	9·78	9·65	9·6
Fat (mm.)	29	30·5	30

TABLE III

Measurement	Difference	S.E. of Difference	C.R.*	Significant	Level of Significance
Comparison of Groups 1 and 2					
Height	1·16	0·4	2·9	Yes	1%
Ponderal index	0·2	0·08	2·5	,,	2%
Biceps	0·65	0·16	4·1	,,	0·1%
Calf	0·45	0·17	2·6	,,	1%
Humerus	0·31	0·06	5·2	,,	0·1%
Femur	0·13	0·12	1·08	No	
Fat	1·5	1·7	0·9	,,	
Comparison of Groups 1 and 3					
Height	0·76	0·22	3·5	Yes	0·1%
Ponderal index	0·22	0·07	3·1	,,	1%
Biceps	0·8	0·07	12·3	,,	0·1%
Calf	0·6	0·04	15·0	,,	0·1%
Humerus	0·22	0·06	3·7	,,	0·1%
Femur	0·18	0·08	2·2	,,	5%
Fat	1	1	1·0	No	

* C.R. = Critical ratio = $\frac{\text{Difference}}{\text{S.E. difference}}$

TABLE IV

Measurement	Difference	S.E. of Difference	C.R.	Significant	Level of Significance
Comparison of Groups 1 and 2					
Biceps	0·64	0·16	4·0	Yes	0·1%
Calf	0·44	0·17	2·6	,,	1%
Humerus	0·31	0·06	5·1	,,	0·1%
Femur	0·13	0·12	1·1	No	
Comparison of Groups 1 and 3					
Biceps	0·79	0·07	12·2	Yes	0·1%
Calf	0·59	0·04	14·8	,,	0·1%
Humerus	0·22	0·06	3·6	,,	0·1%
Femur	0·18	0·08	2·2	,,	5%

Swimmer-canoeists are found to be significantly taller and heavier than the men from the cruiser detachment and those in other branches. Their ponderal index—height (in inches) divided by cube root of weight (lb.)—is significantly lower. Their biceps, calf, and bone measurements are greater in all cases, and significantly so with only one exception—the difference in femur measurements of groups 1 and 2.

Phenotypes

The number and percentage proportions of each sample are given in Table V according to the six sectors

TABLE V

Sector	Numbers			Percentages		
	Central	Peripheral	Total	Central	Peripheral	Total
			Group 1			
543–443	2	1	3	4·9	2·5	7·4
453–343	2	16	18	4·9	39	43·9
354–344	9	5	14	21·9	12·2	34·1
345–334	3	3	6	7·3	7·3	14·6
435–434	—	—	—	—	—	—
534–433	—	—	—	—	—	—
Total	16	25	41	39	61	100
			Group 2			
543–443	2	6	8	3·2	9·7	12·9
453–343	13	14	27	20·9	22·5	43·5
354–344	6	1	7	9·7	1·6	11·3
345–334	3	8	11	4·8	12·9	17·7
435–434	2	3	5	3·2	4·8	8
534–433	1	3	4	1·6	4·8	6·4
Total	27	35	62	43·4	56·3	99·8
			Group 3			
543–443	8	2	10	14	3·5	17·5
453–343	7	6	13	12·25	10·5	22·75
354–344	3	3	6	5·25	5·25	10·5
345–334	6	10	16	10·5	17·5	28
435–434	1	7	8	1·75	12·25	14
534–433	2	2	4	3·5	3·5	7
Total	27	30	57	47·25	52·5	99·75

of primary and secondary component dominance, with a further division into central and peripheral types. The percentage of mesomorphs in each group is shown in Table VI.

TABLE VI

	Test of Significance		Mesomorphs v. Rest Level of Significance
Group 1: 78%	Group	C.R.	
,, 2: 54·8%			
,, 3: 33·5%			
	1 v. 2	2·65	1%
	1 v. 3	4·95	0·1%
	2 v. 3	2·30	5%

Phenotype distributions are also plotted on the conventional two-dimensional somatochart (see Figs. 1–3). This conveys an excellent visual impression of the difference in distribution of the three groups, which may be summarized as follows:

(*a*) Swimmer-canoeists (Fig. 1) are confined to the areas in which mesomorphy is either dominant or strongly represented. Nowhere is it present in less than 4 strength.* Two main groupings appear. One of peripheral endomorphic mesomorphs, and a second of central ectomorphic mesomorphs.

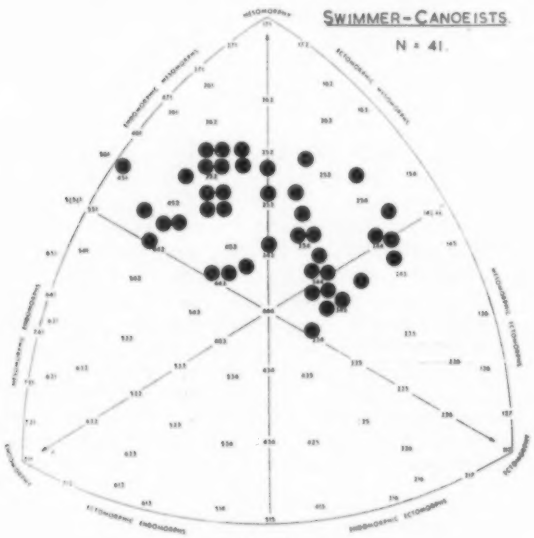

FIG. 1

(*b*) General duty marines appear (Fig. 2) to be rather more evenly distributed. Endomorphic mesomorphy remains predominant as in group 1, but ectomorphic mesomorphy is less strongly represented. Endomorphs and ectomorphs, which were absent in group 1, appear in this distribution.

(*c*) The men engaged in less hazardous trades show a still more scattered distribution, with mesomorphy less often dominant.

The main differences are that group 1 shows no individuals south of the 117–551 gradient, and no individual higher than 5 in ectomorphy or 4 in endomorphy, or lower than 4 in mesomorphy.*

Groups 2 and 3 show individuals up to 6 in ectomorphy and endomorphy and numerous 3s and occasional 2s in mesomorphy.

Individuals less than 4 in mesomorphy or more than 4 in endomorphy and 5 in ectomorphy are unlikely, it seems, to be suitable for swimmer-canoeist training.

*With one exception, a 334.

Conclusions

The graphical and statistical expression of results reveal significant differences in physique between the groups. Less significance may attach to the muscular measurements than the bone in view of the well-known capacity of skeletal muscles to undergo work hypertrophy, but it may be noted that, with the exception of the difference between intercondylar femur measurements in groups 1 and 2, the differences in bone measurements are of equal and in some cases of greater significance than the muscular measurements. As anticipated in terms of Sheldon's thesis, swimmer-canoeists show a higher percentage of mesomorphs than the other two groups.

As a method of selection of suitable trainees, physique estimation has some use in so far as negative conclusions may be drawn regarding their suitability. Thus

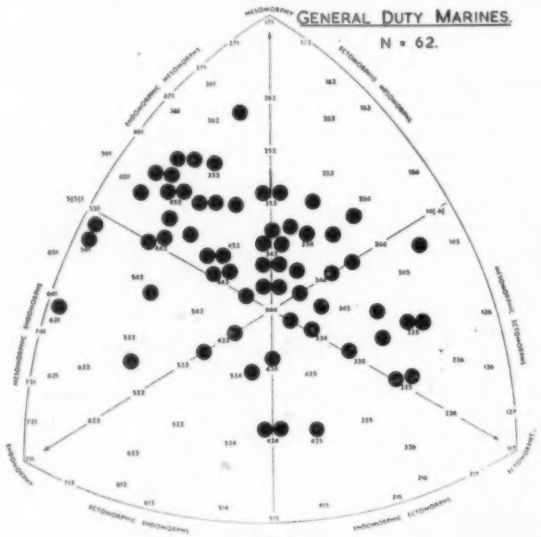

FIG. 2

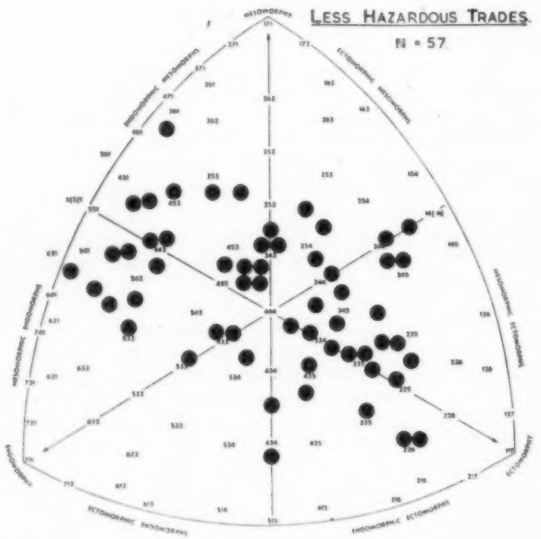

FIG. 3

the demonstration that a candidate is a 452 does not add any useful information regarding his abilities. But if his physique is outside the demonstrated distribution of swimmer-canoeists, it seems unlikely that he will be suitable for training. Experienced instructors probably use this knowledge intuitively, but a prospective study of trainees with progress reports might, it is suggested, prove a useful next step.

Summary

A study has been made of the physique of 160 men serving in the Royal Marines. Those in the more hazardous branches are shown to have a more muscular physique. This is considered to be in keeping with Sheldon's thesis that a relation exists between muscularity and somatotonic traits of temperament.

I wish to acknowledge my thanks to the Medical Director-General of the Royal Navy for permission to publish the above paper and to Dr. R. W. Parnell for his help and criticisms during its preparation.

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REMISSION IN DIABETES

BY

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The tendency to develop diabetes appears to be inherited as a mendelian recessive trait (Joslin, Root, White, and Marble, 1952), but the time of onset and the severity of symptoms vary considerably. In some diabetics, and particularly in the young, there appears to be an absolute failure of insulin production. Plasma studies in these cases show an absence of circulating insulin (Bornstein and Lawrence, 1951), while post-mortem studies on the pancreas fail to demonstrate an insulin content (Wrenshall, Hartroft, and Best, 1954). In diabetics of this type tolbutamide is ineffective, and permanent insulin is necessary to sustain life.

On the other hand, in other diabetics, particularly in obese patients, the circulating insulin appears to be normal, and at post-mortem examination the pancreas can be shown to yield insulin. In such cases the inherited defect may be no more than a functional disability of the pancreas to deal with abnormal stress situations. In potential diabetics this stress is often provided by overeating, but can also be brought about by emotional disturbances, by trauma, by infection, or by pregnancy, for example. Mild diabetes will often remit to an apparently normal state when the stress situation has been removed, as is common experience in obese diabetics following a restricted diet or when an infection has been overcome.

However, some cases of diabetes are neither so severe as to need immediate insulin nor so mild as to respond to simple dietary restriction, and these patients to-day are commonly treated with tolbutamide or similar hypoglycaemic agents. Nevertheless, the decision to put these moderate cases on insulin or tolbutamide is necessarily an arbitrary one, depending on the severity of the diet and the length of observation. As a rule, weight and symptomatology are the deciding factors. The more overweight the patient is compared with normal for his height and age, the more restricted will the diet be and the longer the period of observation before recourse to adjuvant therapy. On the other hand, where the patient is not overweight, where symptoms are troublesome, and particularly when there is intercurrent infection, the sooner will insulin or tolbutamide be prescribed. The decision to put diabetics on insulin or tolbutamide is not irrevocable. Some patients placed on insulin show a decreasing need for it, so that eventually control is by diet alone. In recent trials of oral hypoglycaemic agents (Crowley, Wolff, and Bloom, 1957) it was found that many newly diagnosed diabetics, not responding to diet alone but responsive when tolbutamide was added, remained normoglycaemic and free from urinary sugar after a six-weeks course of this hypoglycaemic agent. Since then all new diabetics not controlled by diet but responsive to tolbutamide have been given a six-weeks course of these tablets, and the tablets were reintroduced only if relapse of the diabetic state occurred.

The purpose of this communication is to define the proportion of new diabetics (1) who have been controlled by dietary restriction alone from the start, (2) in whom dietary restriction was augmented initially by temporary insulin or tolbutamide, and (3) who need permanent insulin or tolbutamide as well as diet. The dangers of unnecessary prolongation of insulin therapy are stressed.

The patients under survey were those referred to the diabetic unit at Whittington Hospital largely during the period of 1952 to 1957, and all have been under observation for at least six months. In all, 1,125 patients with diabetes were referred during this period, but those who were under treatment when first seen are not included, which leaves 550 newly diagnosed cases for review. There were 344 females and 206 males; 287 (52%) were aged 40 to 65, 82 (15%) were younger than 40, and 181 (33%) were older than 65 at onset. The diagnosis was confirmed by a glucose-tolerance curve in all except severe and acidotic cases where the diagnosis needed no confirmation. 100 g. of glucose was administered to the patient in a fasting state, and venous blood sugars were estimated by Hagedorn and Jensen's method in the fasting state, half an hour, one hour, and two and a half hours after ingestion of glucose.

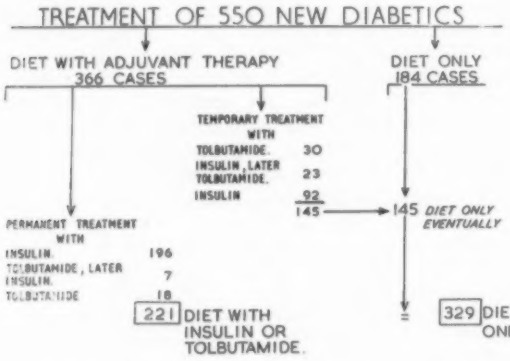
Initial Treatment

Initial treatment varied according to the type of diabetes present (see Diagram).

1. *Diet Alone.*—Mild and overweight diabetics were instructed concerning a 1,200- or 1,500-calorie diet according to the degree of obesity, and were instructed as out-patients to test the urine for sugar, initially three times daily. Control was regarded as satisfactory when the urine became sugar-free and blood sugars were at a normal or near normal range. As a rule the diet was increased up to 2,000 calories when weight had been lost. Diet alone was also tried in more severe diabetics, usually in the ward, except where insulin was indicated as stated below.

2. *Diet and Tolbutamide.*—Where diet alone failed to relieve symptoms and to control glycosuria and

hyperglycaemia as out-patients, cases were admitted to the wards and observed for a further period of five to seven days in the ward on a measured diet. Where hyperglycaemia persisted, tolbutamide was introduced. The length of out-patient observation varied according to the weight of the patient and degree of hyperglycaemia. In an obese mild diabetic on 1,200 or 1,500 calories, observation would extend for several weeks or months before admittance to the ward. On the other hand, more severe cases, not overweight and with heavy glycosuria, would be admitted to the ward as soon as possible. The diet in this group varied from 1,500 calories (approximately 150 g. of carbohydrate, 65 g. of protein, and 70 g. of fat) to 2,200 calories (approximately 232 g. of carbohydrate, 82 g. of protein, and 105



g. of fat). Where tolbutamide led to good control, cases were maintained on it for six weeks, mainly as out-patients, and it was then discontinued. Usually 1 g. was given twice a day initially, it later being reduced to 0.5 g. three times a day or twice a day. In patients in whom relapse occurred when tolbutamide was discontinued, the drug was usually reintroduced.

3. *Diet and Insulin.*—Insulin was used in the previous group of diabetics prior to the introduction of the sulphonylureas. Since then insulin has been used in diabetics in whom there was infection or gangrene, in diabetics who failed to respond to tablets, and in severe diabetics whose urine contained acetone. Diet in this group varied according to the patient's size, activity, and age, and lay between 1,500 calories and 2,800 calories (approximately 312 g. of carbohydrate, 102 g. of protein, and 127 g. of fat).

Later supervision at the clinic depended on the type of therapy employed. Under ordinary circumstances those who appeared to be adequately controlled on diet alone were seen two, three, or four times a year, whereas those on insulin were seen each month or each two months, depending on stability. Diabetics on tolbutamide were seen each week initially, and each week after discontinuation of the drug. This interval was lengthened if it became apparent that diet alone was offering good control.

Results

With these criteria, 184 out of 550 new diabetics were adequately controlled by diet from the start and have not relapsed during the period of observation, varying from a year to over six years. Urine has been sugar-free and blood sugars have been normoglycaemic or near normoglycaemic. In the remainder, adjuvant therapy in the shape of insulin or tolbutamide was necessary. It should be made clear that the number of patients treated with tolbutamide or with insulin bears no relation to the relative place of these two agents in therapy, since tolbutamide has been available for only the last few years of this survey.

Tolbutamide

Seventy-eight diabetics, having failed on simple dietary restriction, were treated successfully with tolbutamide and were maintained on this therapy for six weeks. Of these 78, 25 relapsed with glycosuria and hyperglycaemia after periods varying from a week to six months after the tablets were discontinued. In 18 of these patients tolbutamide was reintroduced and good control again obtained on a maintenance dose of 1 to 2 g. daily in divided doses. In the other seven control was effected with insulin. This means that, of 78 diabetics treated with a six-weeks course of tolbutamide, 53 have so far remained satisfactorily controlled on their dietary regime for periods of from four months to as long as 18 months after the tablets were discontinued. The following are three illustrative cases:

Case 1.—Man aged 57. Diagnosed October, 1956, with symptoms of thirst, polyuria, cramp in the legs, blurring of vision, pruritus penis, and white staining of clothes after micturition. Tolerance curve after 100 g. of glucose: fasting blood sugar, 200 mg./100 ml.; half-hour after, 298 mg.; 1 hour after, 355 mg.; 2½ hours after, 336 mg./100 ml. Height 5 ft. 9 in. (175 cm.). Clothed weight 11 st. 12 lb. (75.3 kg.). Observed for a week in ward on 1,800-calorie diet; blood sugars persistently raised, about 45 g. of sugar daily in urine. Tolbutamide introduced with good results; blood sugars became normal, urine sugar-free. Tolbutamide maintained at 1 g. b.d. for six weeks and discontinued in December, 1956. Diet increased to 2,000 calories, urine remained sugar-free. Last visit July, 1958, weight 11 st. 3 lb. (71.2 kg.). Mid-afternoon blood sugar 154 mg./100 ml. Feels fit.

Case 2.—Woman aged 65. Diagnosed June, 1957. Thirst, polyuria, lassitude, paraesthesia, pruritus vulvae, and lost about a stone (6.4 kg.) in weight over previous year. Glucose-tolerance curve 129, 306, 350, 407 mg./100 ml. Height 5 ft. 5 in. (165 cm.). Clothed weight 10 st. 13 lb. (69.4 kg.). Observed in ward for one week on 1,800-calorie diet; blood sugars remained raised, daily sugar in urine about 16 g. Tolbutamide introduced successfully and maintained for six weeks. Since then sustained on diet only. June, 1958, weight 10 st. 1 lb. (68.5 kg.), urine sugar-free, mid-afternoon blood sugar 124 mg./100 ml.

Case 3.—Man aged 56. Diagnosed October, 1956. Thirst, polyuria, lassitude, paraesthesia, cramp in legs, change in vision, and loss of 2½ st. (17.5 kg.) in weight over the previous year and a half. Glucose-tolerance curve 197, 326, 424, 333 mg./100 ml. Height 5 ft. 9 in. (175 cm.). Clothed weight 13 st. 3 lb. (83.9 kg.). Observed in ward for nine days on a 1,500-calorie diet. Urine showed acetone (Rothera) and daily sugar about 40 g. Blood sugars remained elevated. Tolbutamide introduced successfully and continued until December, 1956. Since then controlled on 2,000-calorie diet only. June, 1958, weight 12 st. 8 lb. (79.8 kg.), urine sugar-free, blood sugar 111 mg./100 ml. Feels well.

Insulin

Insulin was deemed necessary in 318 newly diagnosed diabetics for the reasons given. Where there was no infection, patients usually spent about five days or so in the ward for the initiation of treatment and for instruction on diet, self-administration of insulin, and urine-testing. During subsequent supervision at the diabetic clinic, insulin dosage was reduced in patients

complaining of hypoglycaemic symptoms or in those where urine tests were always sugar-free and where blood-sugar levels were normoglycaemic or hypoglycaemic. In this way insulin requirements of 154 patients were seen steadily to fall over periods varying from a few weeks to over two years and it was eventually discontinued. Of these 154 patients 62 gradually relapsed while on their dietary regime alone; insulin was restarted in 39, while tolbutamide was successfully introduced in 23. This means that, of 318 diabetics in whom insulin was deemed necessary as initial therapy, it was gradually withdrawn in 92 patients. These have subsequently been controlled on a simple dietary regime, as in the following examples.

Case A.—Woman aged 42. Diabetes diagnosed February, 1953, following a month's history of thirst, polyuria, and severe pruritus vulvae. Had one miscarriage, and one healthy baby, birth weight 8½ lb. (3,855 g.). Patient's mother has diabetes. Clothed weight 10 st. 2 lb. (64.4 kg.). Height 5 ft. 1 in. (155 cm.). Urine contained 2% sugar but no acetone. Glucose-tolerance curve 160, 170, 240, 300 mg./100 ml. Admitted to ward for a week and in view of symptoms placed on diet and given insulin. Discharged on mixture of 20 units soluble and 10 units zinc-protamine insulin. At subsequent attendances at the clinic, urine sugar-free and blood sugars in range 180 to 98 mg./100 ml. Insulin steadily reduced and finally discontinued in February, 1955, two years after it was started. Her weight was 8 st. 8 lb. (54.4 kg.). Since then seen about every four months at clinic; urine free from sugar and an afternoon blood sugar in March, 1958, was 157 mg./100 ml. Feels well in herself and keeps to diet: weight 8 st. 5 lb. (53.1 kg.).

Case B.—Man aged 45. Diabetes diagnosed March, 1951, following a three-months history of thirst, polyuria, lassitude, loss of a stone (6.4 kg.) in weight, and cramp in the legs at night. Father died of diabetes. Weight 12 st. 1 lb. (76.7 kg.), height 5 ft. 7½ in. (171.5 cm.). Urine contained sugar and acetone. Glucose-tolerance curve 158, 241, 270, 254 mg./100 ml. Admitted to ward for instruction on diet (2,000 calories) and urine-testing. After two days' persistent glycosuria, insulin started; good control as outpatient on 16 units soluble plus 8 units zinc-protamine insulin. At subsequent clinic attendances urine sugar-free and blood sugars in range 120 to 90 mg./100 ml. Insulin gradually reduced and finally discontinued in March, 1952, a year after it was started. Weight 12 st. 1 lb. (76.7 kg.). Has attended clinic about every four months since then, urine largely being free from sugar. March, 1958, weight 10 st. 10 lb. (69.9 kg.), afternoon blood sugar 134 mg./100 ml.

Further analysis of these patients in whom insulin was discontinued shows that initial insulin requirements varied from 20 to 46 units, the majority being controlled by 24 to 30 units. 40% have been under observation for more than four years, 16% for more than three years, 27% for more than two years, and 17% for more than a year since discontinuation of insulin. The majority are still under clinic care, but in some the period of observation was terminated by default of attendance or by death. While on insulin, 72% showed no marked change in weight, 18% gained more than half a stone (3.2 kg.), and 10% lost more than half a stone (3.2 kg.). After insulin was discontinued, 63% kept a steady weight, 23% lost more than half a stone (3.2 kg.), while 14% gained more than half a stone (3.2 kg.).

Dangers of Therapy

Tolbutamide

Since its introduction, tolbutamide has been extensively used in the treatment of mild diabetics and so far no serious toxic effects have been reported. Nevertheless, wide experience with the drug does not extend more than a few years and long-term toxic effects may yet appear.

Insulin

Apart from the well-recognized symptoms of acute hypoglycaemia, continued depression of the blood sugar can lead to insidious cerebral changes which may persist even after the blood sugar has returned to normal. These changes are particularly likely to occur in elderly patients and particularly when long-acting insulin is used. Jones (1947) has used the term "post-hypoglycaemic encephalopathy" to describe this condition, and two illustrative case histories follow.

Case I.—Woman aged 63. Diabetes diagnosed eight years previously and patient had self-administered a mixture of 24 units soluble and 24 units zinc-protamine insulin each morning. Had not attended clinic. Husband gave a history of repeated attacks of loss of consciousness, relieved by sugar, and bouts of kicking and screaming over the previous few months. For two days before admission she had been in a state of confusion and had had no insulin on day of admission. On examination was drowsy and disorientated, with spastic limbs and extensor plantar reflexes. Carotid pulses palpable and equal; no papilloedema. B.P. 195/100. Lipodystrophy at injection sites. Eczematous vulvo-vaginitis. Urine: no sugar, no albumin. Blood sugar: 124 mg./100 ml. C.S.F. normal. W.R. negative. Progress: 50 g. sugar intravenously led to definite improvement in her mental state, though this was not sustained. Blood and urinary sugar increased during day and insulin started again next day. Subsequently good control on 20 to 30 units insulin zinc suspension daily. Remained confused, incontinent, and spastic for about 12 days, then distinct improvement. Improvement maintained; left hospital on 20 units insulin zinc suspension subsequently reduced to 10 units in out-patient department. On this dosage urine largely sugar-free and blood sugars at normal or near normal. Mental state largely recovered; walked well, though plantar reflexes remained extensor. *Conclusion:* Post-hypoglycaemic encephalopathy induced by sustained overdosage of long-acting insulin, the cerebral damage persisting even though the blood sugars became normal or raised.

Case II.—Man aged 75. Diabetes diagnosed five years previously and zinc-protamine insulin 22 units daily self-administered since. Urine always blue or green when tested with "clinitest." Lived alone and seemed confused and incontinent for several days before admission, since when no insulin given. Had not attended clinic. On admission B.P. 200/90; conscious but irrational. Rigidity of arms, leg reflexes not exaggerated, plantar reflexes flexor. Urine free from sugar; blood sugar 86 mg./100 ml. Remained confused and restless for about 12 days. Urine sugar-free throughout, despite no insulin for first time in five years; blood sugar on two subsequent occasions 52 and 63 mg./100 ml. Once showed signs of hypoglycaemic coma but regained consciousness after intravenous glucose. After 12 days began to improve and finally left hospital in full possession of mental faculties. Did not require insulin. *Conclusion:* A mild diabetic in whom hypoglycaemic encephalopathy appears to have been induced by unnecessary insulin. Despite cessation of insulin, his mental confusion persisted for nearly two weeks.

Discussion

With few exceptions young underweight diabetics need continuous insulin therapy. Older, milder, and overweight diabetics respond to simple carbohydrate dietary restriction without adjuvant therapy. Between these two groups there are many diabetics whose cases

are neither so severe as to need immediate or permanent insulin nor so mild as to be satisfactorily controlled by dietary restriction alone.

Insulin is indicated in all young and severe diabetics, in diabetics where sepsis or gangrene exists, and, before the days of sulphonylurea therapy, in diabetics who continued to show glycosuria and hyperglycaemia despite adherence to a suitable diet. The initial or hospital dose of insulin in new diabetics is often higher than that subsequently necessary to control the diabetic state. In some diabetics insulin requirements steadily diminish until eventually control is obtained on dietary restriction alone. If these patients are maintained without adequate supervision on the dosage of insulin originally necessary for control, chronic hypoglycaemia may result. This can be particularly disastrous in elderly patients with a cerebral circulation impoverished by arteriosclerotic changes. In elderly patients relapse in the diabetic state can be less dangerous than the daily injection of insulin when the blood sugar is already below normal.

Since the advent of the sulphonylureas, tolbutamide has been used extensively in patients with a mild maturity-onset type of diabetes who have failed to respond to dietary restriction. In conducting trials of oral hypoglycaemic agents it was observed that many newly diagnosed diabetics responsive to tolbutamide did not relapse when therapy was discontinued after six weeks. This routine has been followed subsequently in new diabetics not responding to diet. The diet varied from 1,200 calories in the more obese patients to 2,200 calories in the underweight. The length of observation on diet alone before tablets varied from several months as out-patients in mild obese cases to five days in the ward for severe cases. Although it is always arguable that some of these patients might have eventually attained normoglycaemia after a more restricted diet and prolonged observation, in practice the disadvantages of a short course of tolbutamide are slight so long as proper emphasis is laid on the need for continued dietary restriction. There is evidence in experimental animals that prolonged hyperglycaemia, however produced, can itself cause permanent diabetes, but this can be averted if hyperglycaemia is not sustained (Dohan and Lukens, 1948). If this is true in man, the sooner the blood sugar is restored to normal the better. Patients who relapse when tolbutamide is withdrawn remain responsive to the drug when it is reintroduced, and thereafter treatment can be continuous.

Interval supervision continues to be necessary after insulin or tolbutamide has been discontinued. Good control of the diabetic state requires normoglycaemia or near normoglycaemia, and not merely freedom from symptoms. Hyperglycaemia may carry with it ultimate dangers of degenerative changes in the arteries, kidneys, eyes, and nerves, and these changes have occurred in apparently mild and symptom-free diabetics where hyperglycaemia was allowed to persist. Although it has been shown that remissions may last for many years, relapse may always occur, especially in the face of carelessness in diet or of infection.

Summary

In 550 newly diagnosed diabetics, 184 (33.4%) were adequately controlled by dietary restriction from the start, while a further 145 (26.3%) were ultimately controlled by dietary restriction alone after temporary treatment with insulin or tolbutamide. The remaining 221 (40.2%) needed permanent insulin or tolbutamide.

The dangers of unnecessary prolongation of insulin therapy are exemplified by two cases of post-hypoglycaemic encephalopathy.

My thanks are due to Miss M. Crowley and her department for the biochemistry results quoted. I am most grateful to Miss G. Weeks for the care she has taken in going through the case records, and to Miss Mason for the preparation of the diagram.

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ATHEROSCLEROTIC BLOCKAGE IN THE LEFT SUBCLAVIAN ARTERY TREATED BY THROMBO-ENDARTERECTOMY

BY

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Since Takayasu (1908) described blockage of the branches of the aortic arch in Japanese women the condition has been reported as "pulseless disease" (Shimizu and Sano, 1951; Caccamise and Whitman, 1952) and "reversed coarctation" (Frøvig, 1946). The simultaneous blockage of the branches of the aortic arch and of the aortic bifurcation reported by Martorell and Fabré Tersol (1944) is the first record of recognition of occlusion at these two levels in a single patient.

The early papers on Takayasu's syndrome give arteritis, syphilis, and trauma as possible origins of the disease, but later reports suggest that atheroma is the most frequent cause. If this be true, the condition comes into line with the usual pathogenesis of arterial occlusion in other areas. Since the introduction of the technique of aortography by percutaneous puncture of the femoral artery (Seldinger, 1953), demonstration of partial or complete occlusion of one of the branches of the aortic arch is possible before the complete syndrome is established (Wickbom, 1957; Towers *et al.*, 1958).

The basis of this report is atherosclerotic occlusion of the first part of the left subclavian artery in a patient which caused gangrene of the fingers of the left hand and in whom, after confirmation of the site of the block by aortography, thrombo-endarterectomy produced a dramatic improvement in the symptoms and signs.

Case Report

The patient, a woman aged 46, complained of pain in the palm and fingers of the left hand. Examination revealed small areas of fading ecchymoses in the left arm, early gangrenous changes in the left finger-tips (most pronounced in the middle finger), and wasting of the left forearm and small muscles of this hand.

She had had symptoms for 1½–2 years before gangrene of the finger-tips appeared. Small areas of ecchymoses were

first noticed on the left forearm, then round the left elbow, and when gangrene of the finger-tips appeared there were resolving areas of ecchymoses on the left upper arm. The patient experienced tingling of the left fingers over a period of 18 months, and for nine months the fingers had been white and cold first thing in the morning and she had a burning pain in the left palm which lasted some hours. Four months before admission there had been persistent pain in the tips of her fingers, especially the left middle finger, apparently initiated by pressure when the patient was squashed in a football crowd.

The left radial pulse was present but diminished, and there was a thrill and systolic bruit over the left subclavian artery. The oscillometer reading in the right forearm was 4, and in the left 2½. The blood pressure in the right arm was 180/95 mm. Hg and in the left 140/75. The electrocardiogram was normal. Radiographs of the cervical spine showed spondylosis, most marked at the level of the sixth and seventh cervical vertebrae. The Wassermann reaction was negative and the erythrocyte sedimentation reaction 13 mm. in one hour. Aortography by percutaneous puncture of the femoral artery (Dr. P. G. Keates) showed that the left subclavian artery was narrowed for a distance of about 2 cm., starting 2 cm. from its origin, but there was good filling of the axillary, left common carotid, and vertebral arteries (Fig. 1).

Operation

Under general anaesthesia (Dr. D. G. Clark) the patient was placed prone, with the left arm dependent. A periscapular incision enabled the scapula to be mobilized forward and upward, and the fourth rib was then resected. After insertion of rib-spreaders the arch of the aorta and its branches, and the structures in relationship to the under surface of the first rib, were identified across the opened pleural cavity. (Fig. 2.) Pulsation was absent from the first part of the subclavian artery as far as the costocervical branch, and could be felt faintly beyond. A block, which seemed to fill the lumen of the artery, and about 2 cm. in length, was felt from just beyond the origin of the subclavian artery to nearly as far as the costocervicalis. The subclavian artery was dissected free from its origin for 6 cm. After the intravenous administration of 40 mg. of heparin the subclavian artery was clamped, and the block

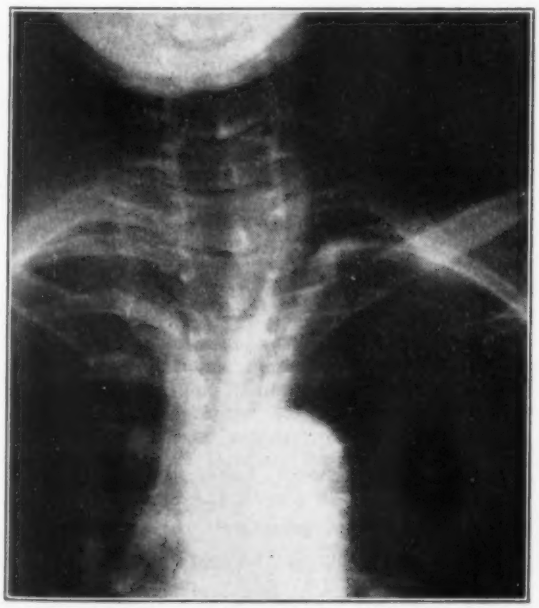

Fig. 1.—Aortogram showing constriction of the first part of the subclavian artery.

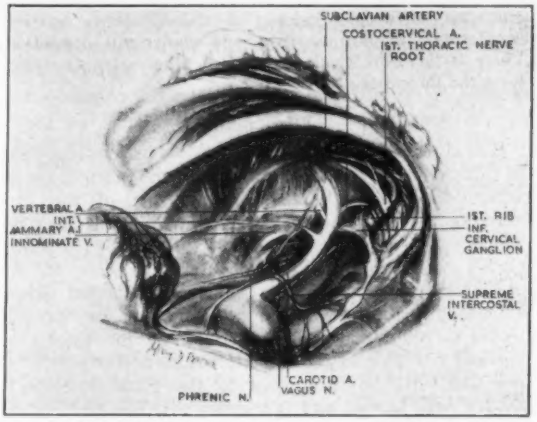

Fig. 2.—View of subclavian artery seen through third interspace.

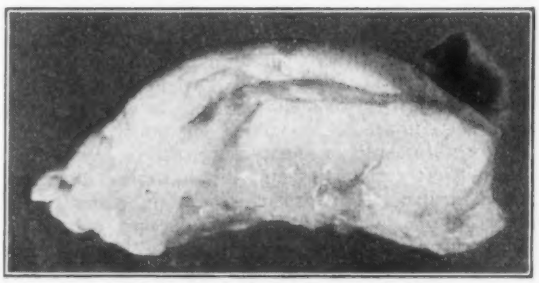

Fig. 3.—Block removed, 2 cm. long.

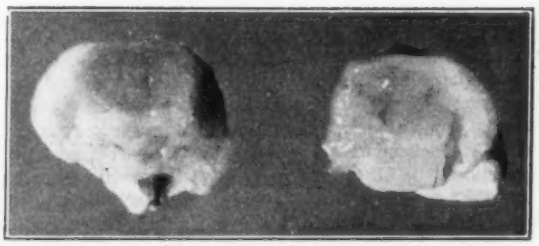

Fig. 4.—Block in section.

(Figs. 3 and 4) was removed through a direct 1½–2-cm. arteriotomy wound. There was a clear plane of cleavage, good back bleeding was established, and the arteriotomy wound was sutured. The pleura was drained through the tenth intercostal space and the thoracotomy and periscapular incisions were closed.

Convalescence was uneventful. The left hand was very warm next day, and the pain in the fingers had disappeared. The thrill over the subclavian artery had disappeared and the blood pressure in the two upper limbs was equal (160/100 mm. Hg). After a few days the temperature of the left hand fell to equal that of the right hand. Eight weeks after the operation the patient was free of symptoms, and the tips of the middle and ring fingers could be separated painlessly.

Histological Report.—Profesor C. E. Lumsden reported on the block removed as follows: "The bulk of the sample appears to consist of hyalinized and partly organized old thrombus, with some calcium in places, but no haemosiderosis. While there is no clear demarcation between the thrombus and the fibrovascular tissue present, and neither endothelium nor muscle is seen, this fibrovascular element

shows such a degree of architectural structure that this layer must be preformed intima; it shows clearly marked proliferation of fibrous tissue and cholesterol deposition. There is therefore clear evidence of atherosclerosis underlying the thrombosis."

Discussion

The clinical picture presented by this patient is similar to those considered to be examples of the thoracic outlet syndrome. Flint (1937) published one of the first accounts of an aneurysm of the third part of the right subclavian artery directly caused by a cervical rib. Eden (1939) reported the cases of three patients having aneurysms to the third part of the subclavian artery extending to the clavicle: in two the cause was thought to be direct damage to the artery by the associated cervical rib, and, in the third, pressure of the artery on the first rib; he subscribed to the thrombo-embolic theory of Lewis and Pickering (1934) to explain associated vascular changes in the hand.

These reports and others put the emphasis on direct damage to the subclavian artery by a cervical or abnormal first rib as the cause of vascular disorders in the upper limb, rather than the effects of irritation of sympathetic nerve fibres. It seemed to be established that a cervical rib or abnormal first rib was the direct agent of damage to the subclavian artery, with consequent thrombosis or aneurysm formation, from which emboli were detached to enter distal arteries. But there are difficulties in this explanation. Many patients have cervical ribs and only a few develop subclavian aneurysms. Cervical ribs are usually bilateral, but subclavian aneurysms are not. Subclavian aneurysms are commonly found proximal to the outer border of the first rib. Resection of a cervical or abnormal first rib, with or without upper dorsal ganglionectomy, seldom gives complete cure, and the use of these procedures in one patient having a cervical rib and subclavian aneurysm did not arrest the progress of the aneurysm (Shucksmith, 1958). In one patient being treated for Raynaud's symptoms in one upper limb no lasting beneficial effect was obtained from cervical rib resection; the other three developed Raynaud's disease, and the upper limb first affected subsequently developed thrombosis of the whole subclavian artery (Shucksmith, 1958).

Shenkin (1957), reporting three cases of thrombosis of the subclavian artery in the presence of cervical rib, described thrombosis of this artery in a 65-year-old patient having bilateral cervical ribs which extended from the origin of the vertebral artery distally to include the brachial artery. Shenkin's and Shucksmith's reports could indicate that primary arterial disease of the subclavian artery could be as much a factor as external pressure on the artery in producing the clinical picture previously ascribed to external pressure alone.

The clinical picture presented in this report indicates clearly that primary arterial disease of the subclavian artery can mimic the picture previously thought to be caused by the external pressure by the scalene muscles or clavicle on the subclavian artery when no cervical rib or band was found. While external pressure as a cause of damage to the subclavian artery with subsequent thrombosis or aneurysm formation is not invalidated, the importance of considering primary arterial disease of the subclavian artery in the costoclavicular syndrome is established. Atherosclerosis was found to be the cause of blockage of the first part of the subclavian artery, and it is possible, on this basis, to explain the formation of an aneurysm of the third part of the subclavian artery by assuming that atherosclerosis involves the whole artery, that atheromatous deposits narrow the first part, and that the loss of elasticity in the distal part allows post-stenotic dilatation.

This concept of atherosclerosis as the primary part of the change in the subclavian artery gains credit when the course of the artery, as seen in the normal arteriogram or directly through the open chest, is studied (Figs. 2 and 5). The subclavian artery courses

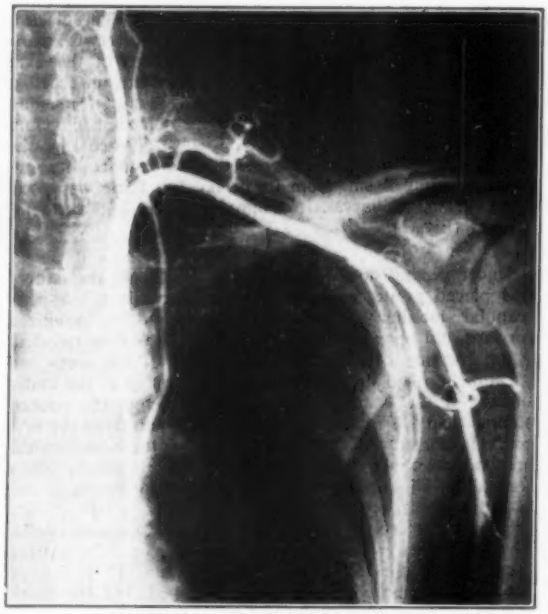

FIG. 5.—Normal subclavian arteriogram.

high into the neck and there arches gracefully towards the arm—a different picture from that seen through the usual exposure at the root of the neck when the artery seems to be dodging between structures which may nip it or lift it up and injure it. Not only is atherosclerosis suggested as a primary cause of lesions in the subclavian artery but it is suggested that coincidental atherosclerosis of arteries in the arm and forearm, together with a similar condition in the subclavian artery, is a possible explanation of wasting of the upper limb and gangrene of finger-tips. Such an explanation would come into line with comparable changes in the lower limb.

Investigation of a patient suffering from arterial disease of the upper limb is not complete without aortography. It must be borne in mind that any atherosclerotic lesion is always more severe than the aortogram may suggest (contrast Figs. 1, 3, and 4).

Summary

The clinical details and successful management by thrombo-endarterectomy of a patient having an atherosclerotic block of the first part of the subclavian artery is described.

It is suggested that atherosclerosis may be the primary cause of change in the subclavian artery previously ascribed to external pressure.

The importance of aortography to demonstrate the branches of the aortic arch in the thoracic outlet syndrome is emphasized.

I am particularly indebted to Dr. C. Groves and Mr. J. C. Coates, of Hull, for referring this patient; to Dr. P. G. Keates and Dr. M. D. Summerling for the aortograms, and to Miss M. Brown for her diagram of the dissected subclavian artery.

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SEQUENTIAL METHODS APPLIED TO THE STUDY OF PROCHLORPERAZINE

BY

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The ability of the pharmaceutical chemists to synthesize compounds of potential therapeutic value in psychiatry is not matched by a corresponding ingenuity in the methods for their clinical evaluation. Consequently the psychiatrist is often baffled by an array of drugs of uncertain therapeutic value and is inclined to criticize the chemist rather than himself for this state of affairs. A need has therefore arisen to develop methods of clinical trial which are rapid and which use simple but reliable criteria of therapeutic effect. Once an overall effect has been established more detailed inquiries can follow. These observations apply particularly to the so-called "tranquillizers"—that is to say, drugs which allay states of over-excitement, such as anxiety and its somatic manifestations, without decreasing alertness and awareness.

Purposes and Design of the Trial

We therefore had two complementary purposes in undertaking a clinical trial of a new tranquillizer. The first was to see if the statistical method of sequential analysis (Armitage, 1954) could be successfully used in a psychiatric drug trial of this kind; if so, the advantages of simplicity in design and of economy in time and numbers of patients treated might be considerable. Our second aim was an attempt to find out whether a new phenothiazine derivative, prochlorperazine ("stemetil"), was as effective in reducing tension and anxiety in psychoneurotic out-patients as some published studies have claimed.

Prochlorperazine is 1-[3-(2-chloro-10-phenothiazinyl)-propyl]-4-methylpiperazine. It is a member of the phenothiazine series of drugs and its effects are similar to those of chlorpromazine. It is prepared for clinical use in two forms, the dimaleate and the dimethane sulphonate. In dosage of less than 40 mg. of the maleate a day side-effects are not troublesome. Jaundice and blood dyscrasias have not so far been reported.

The drug is probably of most use in the management of schizophrenia, but striking claims have been reported for it in the neuroses. Wennersten (1956) quotes unpublished data on 1,429 patients with various neurotic illnesses in whom the response to prochlorperazine was excellent or good in 73%. Vischer (1957) gave the drug to 38 patients with various organic and psychiatric illnesses and claimed that 21 became completely free of psychoneurotic symptoms. Lesse (1957) claims effective relief of 20 out of 37 patients with moderate anxiety, but observed the drug to be less effective with marked anxiety. McAfoos (1957) found all his 37 patients with anxiety reactions helped by prochlorperazine and psychotherapy. Stevenson (1957), in a study of 100 patients of widely different diagnostic categories, claims good relief of anxiety in 83%. Most authors recommend a dose of 15–20 mg. a day and claim that the response is prompt, either within days or one or two weeks. These trials can be criticized on the grounds that they were uncontrolled, the diagnostic categories were ill-defined or ill-assorted, and the criteria of improvement were unclear.

The statistical method, sequential analysis, determined the design of the present trial. A control treatment (placebo) and the new treatment (prochlorperazine) were both given to each suitable patient as he became available. The patient had to decide which of the two treatments he preferred. The sequential plan used had to meet the following requirements. The proportion of response to the placebo was expected to be at least 35% (Beecher, 1956); but if we were able to detect, with a probability of 0.95, a favourable response to prochlorperazine in 70% of patients, this would be considered a sufficient advantage to justify recommending it. The proportion of preferences in favour of prochlorperazine would depend to some extent on the distribution of assessments on the five-point score described below and on the correlation between the two responses from the same subject, but rough calculations suggest that it would be in the region of 0.8. This is the value of θ (the proportion of untied pairs favouring prochlorperazine) which would be obtained if preferences were based purely on favourable responses (rather than the five-point score) and if there were no correlation between the two responses from a subject (cf. Fig. 2 of Armitage, 1954; Snell and Armitage, 1957).

The trial was to be decided on the outcome of this test. As a further exploration of the application of sequential analysis we attempted to use a measurement of anxiety (the clinical symptom which prochlorperazine was most likely to benefit) as the criterion of the effectiveness of the treatments. The appropriate method in such a case is a sequential t-test. The plan chosen to test the null hypothesis that there is no change in the patients' anxiety scores with prochlorperazine at a significance level of 0.05 is described below.

Selection of Patients.—All new psychoneurotic out-patients whose principal complaints were in the opinion of the psychiatrists due to anxiety or tension were considered for the trial. These patients were then given an anxiety questionary on which they had to score 10 or more points in order to enter the trial. The questionary contained 30 items, each of which could score one point. The items were selected from previous investigations of the incidence of subjective and somatic symptoms in anxious psychoneurotics (Cameron, 1944; Eysenck, 1953; Sainsbury and Gibson, 1954). Each item was worded so that it clearly referred to the patient's state during the previous few days.

Administration of Tablets.—Two 5-mg. tablets of prochlorperazine were taken thrice daily for one week and two identical placebo tablets were taken thrice daily during the other week. The order in which the treatments were taken was randomized and was unknown to the doctor prescribing them. As each patient qualified for admission to the trial he was given the next two serially numbered envelopes marked "1st week" and "2nd week," one containing 42 5-mg. tablets of prochlorperazine and the other 42 placebo tablets. The following explanation was given by the doctor: "I want your help in finding which of these two medicines is best for you during the next two weeks, so please follow the instructions exactly so that you can come and tell me whether you prefer those which you took during the first or during the second week when you keep your appointment on . . ." Printed instructions and two questionaries were also stapled to the envelopes issued to the patient.

Assessment of Clinical Effect

The criterion of the tablets' effectiveness was simply whether the patient felt better while taking the first or the second week's treatment. His preference was decided by the answer he gave to the following printed question at the end of each week: "Since you began taking the pills, have you been feeling 'much better,' 'better,' 'no change,' 'worse,' 'much worse'?"

A requirement of the sequential method is that the decision on the success or failure of the treatments must be made on a single criterion, which in this trial was the preference recorded after one week's treatment on each kind of tablet. This limitation was not unfitting, as a simple design was one of our aims, and the patient's preference is an appropriate criterion for a tranquillizer intended for out-patients in whom a subjective impression of improvement is the effect most sought.

A more objective measure of clinical effect was attempted, however. As previously stated, in order to enter the trial the patient had to score 10 or more on an anxiety questionary. The patient was asked to complete the same questionary at the end of the first and again at the end of the second week, and the difference between his anxiety score with prochlorperazine and placebo was recorded (see Table) as it became known.

Statistical Assessment

A feature of the sequential method is that the results are plotted on a graph as they become known (Fig. 1). If, for example, prochlorperazine is preferred by the patient, this is marked as one step in a north-east direction, but if the placebo is preferred it is marked one step in a south-east direction; should the result be a "tie"—that is, they are equally preferred or neither is preferred—the graph is not marked. The results are plotted in this manner until the path on the graph reaches one of its boundaries; the upper one indicating a decision in favour of the new treatment, the lower in favour of the placebo; while the middle boundaries indicate that there is no important difference between the two. How these boundaries are drawn will depend upon three specifications. The investigator must first decide on the chance he is prepared to take of recommending the new treatment when, in fact, it is no better than the old (or placebo in this case). We specified the customary 5% level. Similarly he should also state the risk he will take of failing to recommend the new treatment when it really is an advantage. The other specification is the value of θ, the proportion of preferences in favour of prochlorperazine which would be considered a definite medical gain and which, therefore, should not be missed. As explained above, we set this at 0.8. Having chosen these critical values, a table was consulted which gives figures for the equations of the lines A, B, C, and D in Fig. 1 (Armitage, 1954, p. 263).

Anxiety Scores With Prochlorperazine and Placebo, and Data for Plotting Path of Sequential t-Test

(1) Patients (n)	(2) Anxiety Scores of Patients: Prochlorperazine	(3) Anxiety Scores of Patients: Placebo	(4) Difference (d) Prochlorperazine Minus Placebo	(5) Sd	(6) Sd^2	(7) $z=\frac{(Sd)^2}{Sd^2}$
1	19	22	−3	−3	9	1·00
2	11	18	−7	−10	58	1·72
3	14	17	−3	−13	67	2·52
4	17	19	−2	−15	71	3·17
5	23	22	+1	−14	72	2·72
6	11	12	−1	−15	73	3·08
7	15	14	+1	−14	74	2·65
8	19	11	+8	−6	138	0·26
9	11	19	−8	−14	202	0·97
10	8	7	+1	−13	203	0·83
11	21	22	−1	−14	204	0·96
12	18	16	+2	−12	208	0·69
13	19	16	+3	−9	217	0·37
14	18	20	−2	−11	221	0·55
15	19	19	0	−11	221	0·55

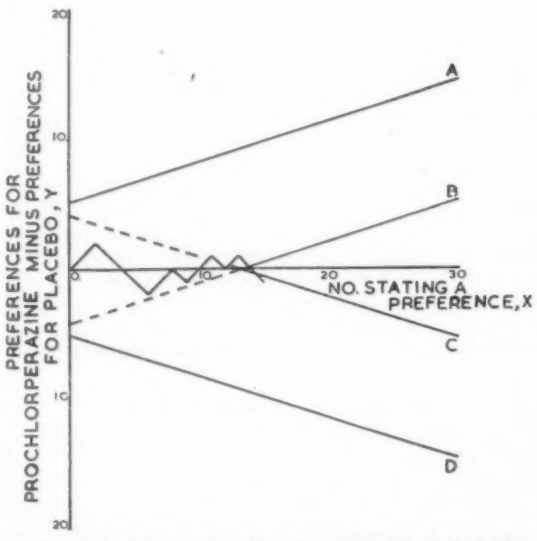

FIG. 1.—Path of the results and the boundaries (A, B, C, D) for a sequential test to detect the difference between two proportions at the 5% level if the preference for placebo is 35% and prochlorperazine 70%.

The significance of the differences between the anxiety scores of the patients on the two treatments was examined by a sequential t-test. This test ". . . can be regarded as one in which the value of Student's 't' is calculated at each stage and plotted against n, the number of pairs. . . . The trial is continued until the sample path formed by joining the successive values of t crosses one of the three boundaries indicating either a significant difference in favour of one or other of the treatments or a non-significant difference" (Armitage, 1954). Instead of t, z is calculated at each stage ($z=(Sd)^2/Sd^2$, where d, in this trial, is the difference between a patient's anxiety score with prochlorperazine and with placebo; Sd is the sum of these differences for all patients so far observed; and Sd^2 is the sum of the square of the differences). With this method the first rule is to make an estimate of δ, the difference between the effects of the two treatments which one would wish to detect (δ = mean difference/s.d. of differences). As we had not the data to do this we referred to Table III in Armitage's paper (1954, p. 267), which gives the critical value of δ that can be detected, with a P of 0.95, if a fixed-sample-size t-test on the mean of 20 differences were used.

This value of δ determined the boundaries of the plan shown in Fig. 2.

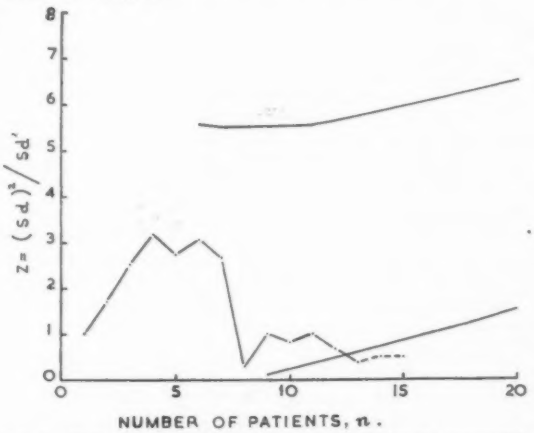

FIG. 2.—Path of the results and the boundaries for the sequential t-test (z is derived from t).

Findings

The patients were all initially diagnosed as suffering from psychoneurotic reactions, with anxiety as the principal symptom. In most of them the somatic manifestations of anxiety were also prominent. There were no notable differences in clinical symptoms between those who preferred prochlorperazine and those who preferred placebo. Their mean ages were 33.0 years and 37.6 years respectively, and their mean duration of illness was 36.4 months and 33.5 months. There was no association between the patient's preferences and the order in which the two treatments were given.

Each patient's preference for prochlorperazine or placebo was made known to us as soon as it was obtained by the doctor. The preferences were then plotted on the diagram shown in Fig. 1. The horizontal axis (x) records the number of patients who expressed a preference, and the vertical axis (y) the number of patients who preferred prochlorperazine minus the number who preferred the placebo.

The middle boundary of the graph was crossed after 14 patients had expressed a preference. At this point the trial was finished. The decision reached, therefore, was that there was no important difference between the two treatments; in fact, the two treatments were equally effective (each was preferred seven times). We have therefore no evidence that out-patients whose predominant complaint is anxiety fare any better when treated with 30 mg. of prochlorperazine daily than with dummy tablets.

The trial was decided by the 14 patients who were able to say which treatment they preferred; six were unable to make a choice between the drugs because neither had any effect. A total of 20 patients therefore entered the trial.

The details and results of the sequential t-test are given in the Table and Fig. 2. The columns in the table are: (1) the patients in serial order; (2) and (3) their anxiety scores with prochlorperazine and with placebo; (4) the differences, d, between these scores; (5) the cumulative total of the differences, Sd; (6) the squares of the previous column; and (7) the z scores. In Fig. 2 the z scores are plotted against the number of patients.

It was found that the lower boundary, which indicated no significant difference between the effects of the treatments on anxiety scores, was crossed when n was 13. Two further patients were added to confirm that the path was continued. This finding is consistent with that obtained when the patient's preference was the criterion of therapeutic effectiveness.

Discussion

Before considering whether the methods used in this trial fulfil our purpose, which is to describe a rapid and reliable method of clinical assay of new tranquillizers, the conclusions reached on the therapeutic value of prochlorperazine is examined.

The finding that prochlorperazine had no appreciably better therapeutic effect than a placebo is valid only for patients in whom anxiety is the predominant symptom; nevertheless it is with this group of out-patients that a tranquillizer is most likely to be successful. The patients received seven daily doses of 30 mg. Though this dose is higher than in most investigations it is still possible that a larger dose might have been more effective. Troublesome side-effects were not encountered. It might also be objected that the optimal effect would not be obtained in one week. A short period of treatment was chosen because previous studies had claimed an effect within a week, but also because the patient had to express a preference. To enable him to do this the duration of treatment had to be brief enough to allow him to make a comparison. Lastly, it is possible, had we stipulated a lower proportion of preferences for prochlorperazine as representing a real advance in therapy, we would then have detected an advantage for it. The previous studies claimed 70% or higher successes with prochlorperazine. As we expected a similar proportion of successes it was economic to choose this figure to represent a real gain in therapy.

More relevant to the question of the value of sequential analysis is the confidence with which the conclusion can be accepted. The probability of reaching the middle boundary when the two treatments are equally effective is 0.95. So the risk of concluding that there is no important difference when, in fact, one of the treatments is superior (by the specified proportion)

is 5%. An advantage of this method is that the risk of making errors of this kind is stated (Bross, 1952).

In both of the methods described the number of patients needed to decide the outcome was less than would be needed, on the average, with the equivalent fixed-sample-size test. This economy in cases is a valuable feature of sequential methods. The small numbers were also determined by the comparatively high proportion of preferences required for the new drug before we were willing to recommend it.

Because the procedure is so simple both methods are well suited to the trial of new drugs in a busy out-patient clinic or admission ward. Suitable patients are observed as they occur in the course of the daily work; the data are analysed without any computation or only one computation with the sequential t-test; and the psychiatrist is only required to assess carefully one crucial clinical characteristic of each patient. The last consideration, however, also imposes a restriction which may limit their application: improvement in the mental state of psychiatric patients must often be assessed on a number of aspects of behaviour. It should be possible to overcome this difficulty by setting up sequential tests for two or three essential clinical features to run concurrently. In our trial, for example, we might have begun by proposing that it would be decided in favour of prochlorperazine only if and when the path in both the sequential test of the patients' preferences and the sequential t-test of the measure of their anxiety crossed the upper boundary, and the decision "no important difference" be made only when the middle and lower boundaries are crossed. Should the upper boundary be crossed on one characteristic and another boundary on the other the result would be inconclusive concerning which treatment is therapeutically superior; but the information obtained would presumably still be a valuable guide to that aspect of behaviour on which the drug's activity is effective.

Conclusions and Summary

In psychiatry there is a need for rapid and reliable methods for the clinical assay of the many new compounds of potential therapeutic value now being manufactured. The method of sequential analysis was considered for this purpose. A trial was therefore undertaken to compare the effectiveness of a new tranquillizer, prochlorperazine, and a placebo in the treatment of anxious psychoneurotics.

After each patient had received each treatment for a week he stated which was preferred. No important difference at the 5% level of significance was found between the treatments when 20 patients had entered the trial.

Each patient also completed an anxiety questionary at the end of each week. A sequential t-test was undertaken and no significant difference was found between the decrease in anxiety scores with each treatment after 13 patients had entered.

It is concluded that in certain circumstances sequential methods are well suited to the early evalution of new psychiatric drugs. They are easier to administer, more economical, and give a more precise decision than conventional tests.

We thank the medical staff of Graylingwell Hospital for their close co-operation and our assistant, Miss P. Ray, for preparing the diagrams. We are grateful to Dr. P. Armitage, of the Medical Research Council's Statistical Research Unit, for his most helpful criticisms of this paper; and to Messrs. May & Baker Ltd., who kindly supplied the stemetil and dummy tablets.

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AN APPRAISAL OF PHENYLBUTAZONE SUPPOSITORIES

BY

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The patient with both rheumatoid arthritis and a peptic ulcer presents a difficult therapeutic problem. Drug therapy for the joint condition, whether with salicylates, phenylbutazone ("butazolidin") and its analogues, or adrenocorticosteroids, may have harmful effects upon the upper gastro-intestinal tract. Aspirin in high or low dosage can cause gastric irritation and probably bleeding (Douthwaite and Lintott, 1938; Muir and Cossar, 1955). Corticosteroids may produce peptic ulcers (Sandweiss, 1954). Similarly, a risk of phenylbutazone is peptic ulceration (Raffensperger, 1953), which can be fatal from perforation (Shield *et al.*, 1953; Beutler and Bergenstal, 1954) or from haemorrhage (Stephens *et al.*, 1952; Benstead, 1953). Phenylbutazone has other complications, such as depression of the bone-marrow and agranulocytosis (Dilling, 1953; Leonard, 1953), skin rashes (Cudkowicz and Jacobs, 1953), stomatitis (Freeland *et al.*, 1953); visceral lesions (MacCarthy and Jackson, 1955), and water retention (Wilkinson and Brown, 1953), which may precipitate cardiac failure in the elderly. However, the toxicity of any drug must be weighed against the benefits conferred by it, and we believe that its use is justified in carefully selected cases of the painful and crippling rheumatic disorders. The avoidance of gastric irritation has been a particular interest, and we report a small clinical trial where phenylbutazone has been given as a suppository rather than as a tablet or by injection.

Material and Methods

There were 26 patients. Nineteen suffered from rheumatoid arthritis; 11 of these also had a duodenal ulcer, two a gastric ulcer, two a hiatus hernia, two had a dyspepsia of unknown origin which made oral therapy impossible, and two developed a dyspepsia on phenylbutazone tablets. Two patients had ankylosing

spondylitis; one with a duodenal ulcer and one developed phenylbutazone dyspepsia. There were five cases of osteoarthritis: two with dyspepsia following phenylbutazone tablets, one with dyspepsia of unknown origin, and two volunteered to have the suppositories, though oral therapy had not been tried. The diagnosis of ulcer had in every case been proved radiologically, and three had previously perforated.

Oral therapy was not abandoned because of dyspepsia unless it was certain that the patient had taken the drug after meals, as this probably lessens the chance of gastric disturbance. A suppository containing 250 mg. of phenylbutazone was inserted into the rectum each night, and occasionally two were used in the 24 hours. Serum phenylbutazone estimations were carried out to assess absorption of the drug from the rectal mucosa. It was found by Currie *et al.* (1953) in a clinical trial involving 424 cases that a serum level of 8–11 mg./100 ml. was optimal for the suppression of symptoms, but that a remission could be maintained at concentrations between 4.6 and 8 mg./100 ml. Bruck *et al.* (1954) claimed that no further clinical improvement is likely if attempts are made to increase the serum level above 10 mg./100 ml., but that there is a rapid increase in toxic side-effects above that figure. The difference in the number of patients with toxic symptoms above and below 10 mg./100 ml. was statistically significant. As a routine we estimate the serum level of phenylbutazone of patients receiving the drug orally and adjust the dose according to the blood levels.

The technique for estimating phenylbutazone was a modification of Pulver's (1950) method. 1 ml. of serum or plasma is added to 10 ml. of acetone, shaken, and allowed to stand for 30 minutes. The acetone extract is then filtered into a 50-ml. conical flask and the precipitate washed twice with 5-ml. portions of acetone. This is carefully evaporated on a sandbath until the solution becomes turbid. 2 ml. of 20% *p*-toluene sulphonic acid is added to the test, to a "reagent blank" containing 1 ml. of water, and to the standards. It is only necessary, in practice, to prepare one standard, of 10 mg./100 ml. 1 ml. of this is equivalent to 0.1 mg. of phenylbutazone actually used in the estimation. The acid mixtures are heated in an oven at approximately 100° C. for not less than three hours. Then 4 ml. of water is added to each and heating continues for another three hours. Either of these heating periods can be extended and the specimens left in the oven overnight, if necessary, without detriment to the result. 20 ml. of water is added to the dry residue and filtered (Whatman No. 42), repeating if necessary until the filtrate is clear. To a 5-ml. aliquot of the filtrate is added 1 ml. of 0.1% sodium nitrite, with shaking; allow to stand for three minutes. Next add 1 ml. of 0.5% ammonium sulphamate, with shaking. Wait two minutes. Finally add 1 ml. of 0.1% naphthyl-ethylenediamine dihydrochloride, mix, and allow to stand for two minutes. The resulting coloured solutions are read within five minutes in a photoelectric colorimeter, using an Ilford 605 filter. The result is calculated as follows (RT is the reading of unknown and RS the reading of standard):

$$\text{Phenylbutazone} = \frac{RT}{RS} \times 0.1 \times \frac{100}{1} \text{ or } \frac{RT}{RS} \times 10 \text{ mg./100 ml.}$$

Analyses were routinely carried out in duplicate and the mean value was reported. The average deviation from the mean occurring in 20 consecutive specimens was ±4.25%. It is essential to put up a phenylbutazone standard with each batch of estimations rather than to rely on results read off from a prepared table or graph, as colour development varies with the freshness of the reagents. It also has to be remembered that sulphonamides will interfere with the colour development and give erroneously high results. The method needs no special apparatus, and can be carried out in any clinical laboratory.

Results

Phenylbutazone is rapidly absorbed from the rectum, as shown when serum levels are estimated at intervals of two, four, and six hours after a suppository containing 250 mg. (Fig. 1). The actual height of these initial readings can be discounted, as there is a progressive increase in the serum levels over the first few days until a plateau level is reached at the end of 7 or 10 days. Readings after this period are fairly constant for the individual and probably depend upon individual differences in the rate of metabolism of the drug rather than varying rates of excretion in the urine (Burns *et al.*, 1953). The serum levels obtained with rectal phenylbutazone are comparable to those from the oral route (Fig. 2).

When the 26 patients were maintained on a single suppository daily, it was found that 12 had a serum phenylbutazone level above 8 mg./100 ml.; 10 kept a level above 4.6 mg./100 ml., and most of these had satisfactory relief from pain; increase to two suppositories daily raised the serum level to a more

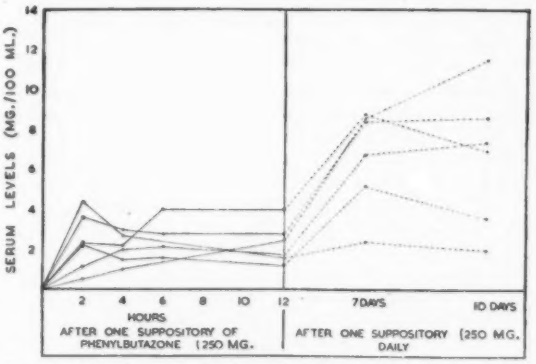

FIG. 1.—Showing rapid absorption of phenylbutazone after administration of one suppository daily.

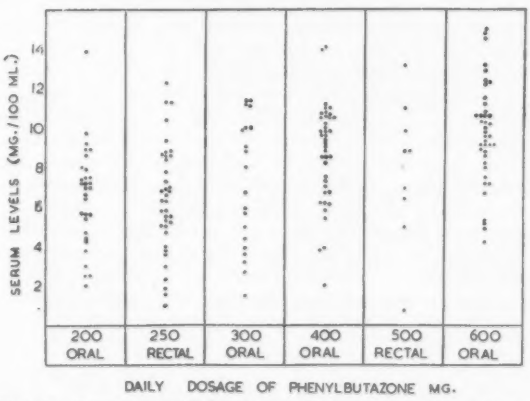

FIG. 2.—Serum phenylbutazone levels estimated on 100 patients receiving the tablets and on 26 treated by suppositories.

effective therapeutic range. Four patients had low levels between 1 and 4 mg./100 ml.; two of these were raised satisfactorily by doubling the suppositories, but the other two still maintained too low a level. This last fact is a well-known problem, and occurs in spite of massive oral or intramuscular doses. It is not due to an increased excretion in the urine or deposition in the tissues, but, more likely, results from a greater rate of metabolism of the drug in certain subjects (Burns *et al.*, 1953).

Six patients received the suppositories for periods of one year or longer, 12 for six months or longer, and eight for short periods of six months or less. Once the plateau level of phenylbutazone is obtained, the serum level remains constant, and only slowly declines over a period of 14 days when the drug is discontinued. Thus only one dose is necessary in the 24 hours. This is the same with the rectal route, and was confirmed by means of diurnal variations of the serum level in three patients. Von Rechenberg (1953) used phenylbutazone suppositories for short periods in five patients and obtained serum levels similar to our figures.

There was no practical difficulty in insertion of the suppositories except in patients with severe deformity of the hands; then a nurse or relative could do this instead. Local effects from the suppositories were noted in two cases; one had a transient pruritus, which disappeared though the drug was continued; the other developed diarrhoea, but there was no recurrence of this when the suppositories were begun again later. Sigmoidoscopy was performed in six patients who had received suppositories for periods longer than three months, and the rectal mucosa appeared normal. Rectal biopsy was done in four, the histology being also normal.

Phenylbutazone dyspepsia disappeared when the suppositories were substituted for the tablets, and none of the 13 patients with proved peptic ulcers had any activation of their symptoms, though four received the drug for longer than one year continuously. The purpose of this trial was to demonstrate that phenylbutazone can be given effectively by the rectal route rather than to assess the therapeutic effectiveness, which has been done previously on large series; pain relief is claimed in approximately 80% of cases (McMahon, 1957; Kelly, 1954). Rectal administration has perhaps been neglected. It is preferable to intramuscular injection of the drug, which is painful and particularly difficult for these patients with their wasted muscles and deformed hands.

In our series, pain relief correlated moderately well with serum level, though some patients have adequate serum levels with no clinical effect, a fact that is unexplained. Systemic toxic effects are to be expected with the same frequency whether phenylbutazone is given orally, parenterally, or rectally. This occurred in one patient, a woman with rheumatic heart disease in whom early cardiac failure was precipitated owing to salt and water retention but disappeared rapidly after withdrawal of the drug. Slight oedema of the ankles of no serious significance occurred in two others, but was controlled by a low-salt diet. No patient showed any depression of the white blood cells, a complication which is probably no more common than with gold therapy.

Discussion

The pathogenesis of dyspepsia following oral phenylbutazone therapy is not completely known. A direct irritant effect upon the gastric mucosa is probably the sole cause in many cases, giving a picture of multiple superficial gastric erosions (Raffensperger, 1953). The aggravation of existing peptic ulcers, which is a striking lethal complication of oral therapy, probably occurs through increase of the basal gastric secretion (Kirsner and Ford, 1955). The drug usually increases hydrochloric acid production when given orally, and may to a less extent do the same after intramuscular injection. This latter fact would explain the occasional instances where parenteral phenylbutazone has caused haematemesis (de Sèze, 1953) and this could obviously occur with rectal administration. Fortunately it has not yet happened in our experience. We regard the suppository as a useful route of administration in cases where gastric symptoms or peptic ulcers make oral administration either dangerous or impossible.

Summary

Phenylbutazone suppositories can be used as the sole therapy where oral administration is contraindicated.

Absorption of phenylbutazone from the rectum is adequate, as shown by serum levels of the drug.

This work was carried out at the Highfield Hospital, Droitwich, and appreciation is given to the nursing staff for their careful co-operation. Grateful acknowledgments are made to Mrs. P. K. Limerick, Miss E. M. Skyme, and Miss P. A. Goodyear for technical assistance; also to Geigy Pharmaceutical Company Ltd. for supplying the pure phenylbutazone from which the analytical standard was prepared. The technique for estimating phenylbutazone was a modification of that of Pulver (1950) developed by Dr. Ena Bruck (West London Hospital, 1953).

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The 14th Congress of the Scandinavian Neurological Association was held in Helsingfors last year at the invitation of the Finnish Neuro-Psychiatric Society, and its proceedings have now been published. The main subject of the Congress was the late sequelae of traumatic brain injuries, and delegates were taken to visit special homes for veterans injured in this way. It was decided that the next Congress should be held in Denmark in 1960. (*Acta Psychiatrica et Neurologica Scandinavica, Supplementum 137, Volume 34, 1959.*)

Medical Memoranda

Submucous Lipoma of the Jejunum

Submucous fatty tumours of the gastro-intestinal tract are rare. Comfort (1931) was able to review 181 examples, and Schottenfeld (1943) quoted 275. Smith and Mayo (1950) traced 67 lipomas of the small intestine in the surgical and necropsy records of the Mayo Clinic, 53 of which were found at necropsy and were probably symptomless, 5 were incidental findings at laparotomy, and 9 were producing symptoms that required surgery. The tumours were distributed as follows: ileum 42%, duodenum 30%, jejunum 25%, and Meckel's diverticulum 3%. The nine cases needing surgery were all in the ileum, two causing painless rectal bleeding and the others intussusception. Six of the latter had the additional feature of epigastric distress and one was confidently accepted as a case of peptic ulcer. The successful operative treatment of an intussusception due to an ileal lipoma is described by Ellis and Windham (1952). The patient, a negress aged 71, had suffered from abdominal cramps and bouts of nausea or vomiting since adolescence.

Multiple lipomata in the stomach have been described by Fawcett, Bolton, and Geever (1949), and in the duodenum by Palazzo (1948), Hoffman and Grayzel (1945), and Kirkland and Boyer (1951). Findley and Thompson (1956) reported multiple lipomata of the ileum.

Case History

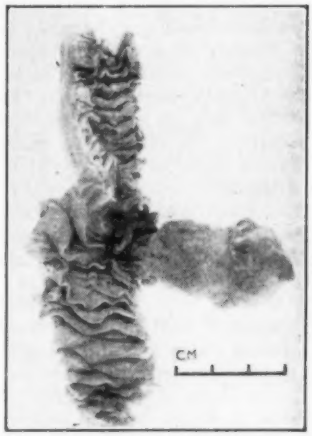
A man of 50 was admitted to hospital with a history of violent abdominal pain in the region of the umbilicus six weeks previously. He vomited "bile and acid" on three occasions and attended his doctor a week later. There was no history of previous indigestion, and the pain was not related to food. He lost 14 lb. (6.4 kg.) in weight over the six weeks before admission. Investigation showed a haemoglobin level of 56% with a moderate hypochromasia. Stools were consistently positive for occult blood, and fractional gastric analyses showed a complete absence of free HCl and a low total acidity. Barium-meal *x*-ray examination revealed a normal appearance of the oesophagus, stomach, and duodenum. In view of the short history, loss of weight, persistent occult blood in the stools, and achlorhydria, laparotomy was advised, with a tentative diagnosis of early carcinoma of the stomach.

Operation.—Through a midline upper abdominal incision the stomach and duodenum were found to be normal. The proximal jejunum was hypertrophied, and on tracing this downwards a tumour was felt in the bowel attached to the mesenteric wall about 3 ft. (90 cm.) from the duodenojejunal junction. The mesentery opposite the tumour showed a triangular zone of fibrotic induration, the base of the triangle being the attachment to the bowel with the apex tapering to the base of the mesentery. The rest of the mesentery was normal. Because of the fibrotic zone a wide resection was carried out to include the whole of it, and 20 in. (50 cm.) of the jejunum was removed, the tumour lying at its mid-point. An end-to-end anastomosis was carried out and the abdomen closed. The patient recovered uneventfully from the operation.

Pathology.—The tumour was cylindrical, 7 cm. long, 2 cm. in diameter, and attached to the intestinal wall by a pedicle 1 cm. in diameter (Fig.). For a distance of 1.5 cm. the free end was slightly swollen and the surface ulcerated. Histological section showed that the ulcerated area was coated with fibrinopurulent debris and that the core was composed of mature adipose tissue supported by coarse fibrous strands. Section through the pedicle showed a deposit of dense inactive fibrous tissue between the mucosa and the muscle.

Comment

The only previously reported case of a submucous lipoma of the jejunum causing symptoms is that described by Cavanaugh and Mills (1956). A woman aged 55 had a violent attack of general abdominal pain during a meal. The pain subsided in a few days but recurred five days later and then continued for six days; during this time she vomited repeatedly and had no bowel action. She was admitted to hospital and treated with intravenous fluids and gastric lavage. The introduction of barium into the stomach showed an obstruction in the upper jejunum. At operation the obstruction was found to be a fatty tumour measuring 8 by 3 cm. with a pedicle 1 cm. in diameter, a structure approximately the same size and shape as the one we have encountered. The tumour seen by Cavanaugh and Mills also had extensive surface ulceration.



Photograph of the tumour.

Their case, however, was under suspicion as being of intestinal origin from the time the patient entered hospital, whereas ours was regarded as being probably due to a carcinoma of the stomach. It is of importance to recall that in one of Smith and Mayo's cases, where the tumour was in the ileum, a diagnosis of peptic ulcer was made and that six other cases experienced epigastric distress. There is evidently a real danger of attributing the symptoms caused by these fatty tumours of the small gut to some gastric condition.

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Reviews

NEW SURGICAL MATERIALS

Modern Trends in Surgical Materials. Edited by Leon Gillis, M.B E., M.Ch.(Orth.), F.R.C.S.(Eng.), F.R.C.S.(Edin.), D.L.O. (Pp. 275+xi; illustrated. 72s. 6d.) London: Butterworth. 1958.

This book contains knowledge of interest to every surgeon in whatever field he may work. Chapters are contributed on new materials used in various branches of surgery by surgeons who are known authorities in their fields. What are perhaps even more valuable are the chapters contributed by the non-medical scientific experts on such subjects as metals and plastics used in surgery. The chapter on plastics by the head of the Plastics Division of Imperial Chemical Industries is a particularly clear review of the basic knowledge about these substances. Orthopaedic surgery, and particularly the reactions, both physical and chemical, which arise when metals are implanted into bone, are more fully dealt with than other subjects.

A field that might profitably be covered in a subsequent edition is the reaction between blood or infusion fluids and the materials of the containers or conduits through which they may pass during infusions, transfusions, or perfusions. The enormous advances made in recent years in perfusion, either of the whole body as in open cardiac surgery, or in parts of it when, for example, a limb may be perfused with blood containing substances active against cancer, have raised many problems of this sort. A review of the effects upon blood of contact with metals, silicones, and plastic materials of other sorts would be most valuable.

This book is greatly to be recommended for use for basic reference as well as for pleasurable and profitable browsing.

J. B. KINMONTH.

VECTORCARDIOGRAPHY

Atlas d'Électrocardiographie et de Vectocardiographie. Étude du Ventriculogramme dans les Conditions Normales et Pathologiques. By Pierre W. Duchosal and Jean R. Grosgurin. (Pp. 181; illustrated. Sw. fr. 23.) Basle, New York: S. Karger. 1959.

This book is the distillation of many years' work and experience by the authors in the field of vectorcardiography. By presenting examples of normal and abnormal electrocardiograms and vectorcardiograms it shows how these two methods are complementary, each amplifying the information afforded by the other. The authors believe that the intrinsic value of the vectorcardiogram lies in its clarity of representation, and the illustrations in this book amply justify this premise. Electrocardiograms and vectorcardiograms are welded together to tell one story, the electrocardiographic pattern at once becoming simpler and more fully understood by reference to the vectorcardiogram.

The impact of modern vectorcardiographic theory on the interpretation of the electrocardiogram is discussed, with particular reference to the theories about the "electrical position" of the heart, that describe its vertical or horizontal site and the direction of its rotation. Spatial vectorcardiography shows that such variations are sometimes due to variations in the shape of the QRS vector loop itself, and not to the position of the loop in relation to the body. Similarly, the essentially relative meaning of the words "intrinsicoid deflection," as applied to the precordial leads, is stressed, for such leads are shown to reflect general as well as local potentials in the heart, the broad pattern of each lead conforming to the general shape of the vector loop. The intrinsicoid deflection should, therefore, not necessarily be regarded as a true guide to the exact time of electrical activation of the underlying cardiac muscle.

Perhaps the most striking element of the book is the way in which the diversity of individual cardiograms, whether in health or disease, is brought home to the reader. This diversity is not always obvious on first inspection of the electrocardiogram, for two rather similar electrocardiograms may be accompanied by strikingly different vectorcardiograms. The authors conclude that variations in the individual morphology of the spatial vectorcardiogram are due to differing combinations of simultaneous centres of electrical activity within the heart, these in turn being dependent on the individual architecture of each heart and on the particular path of propagation of the electrical stimulus in that heart.

The atlas is refreshing to read, for it not only throws light on certain obscurities of the electrocardiogram, but also emphasizes how much more we need to know about the causes of individual variations in the form of the QRS complex.

PATRICK MOUNSEY.

THE VINEYARD OF SURGERY

To Work in the Vineyard of Surgery. The Reminiscences of J. Collins Warren (1842–1927). Edited by E. D. Churchill, M.D. (Pp. 288+viii; illustrated. 40s.) Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1958.

John Collins Warren, the author of these interesting reminiscences, was a member of the illustrious Warren medical dynasty. From 1782 to the present day, with scarcely an interval, Warrens have taught anatomy and surgery at Harvard, and have been staff surgeons of the Massachusetts General Hospital since its opening in 1821.

John Collins Warren served as a medical student in Army hospitals during the Civil War and graduated M.D. Harvard in 1866. He then had a prolonged study tour in Europe, spending most of his time in Vienna and Berlin, working under Cohnheim, Billroth, and Virchow. In London he saw the work of the chief surgeons—Paget, Férgusson, Timothy Holmes, Erichsen, and Henry Thompson. His account of the lithotrite kept up Thompson's coat-sleeve, a vector of cystitis from one patient to another in those pre-antiseptic days, makes one shudder. Warren visited Lister in Glasgow and was greatly impressed by his teaching, although, faced with reactionary opposition on his return to America, he had little opportunity of applying it until he was appointed a visiting surgeon at his hospital in 1876 and then professor of surgery at Harvard Medical School. With Professor Henry P. Bowditch he became one of the chief promoters of the growth of the school.

The editor, Dr. Edward D. Churchill, a distinguished Harvard surgeon, has done his task well. He supplies copious biographical and historical notes, and writes a sequel which completes the history of Harvard and its associated hospitals to the present time. In Appendix II he describes the beginnings of the Harvard Cancer Commission, which Dr. Warren initiated. This book, whose title is taken from the writings of William Clowes (1544–1604), is a valuable contribution to the history of surgery in America. It is well produced and illustrated.

ARTHUR S. MACNALTY.

SWEDISH MEDICAL ASSOCIATION

Svenska Läkaresällskapet 150 År; dess Tillkomst och Utveckling. En Återblick. By Hilding Bergstrand. (Pp. 562; illustrated. 50 Sw. kr.) Stockholm: Svenska Läkaresällskapet. 1958.

This book commemorating the 150th anniversary of the Swedish Medical Association records the origin and development of the association. It describes the medical world of thought at the time of its foundation and follows its development by means of the records and publications of the association. The mass of material available has rendered drastic selection necessary. To avoid duplicating information given in two earlier works on the history of the association up to 1938, the author has dealt with four main problems more thoroughly than had previously been done.

The changes in the treatment of several diseases of particular interest are reviewed in the light of what has happened since their first appearance in the annals—cholera, dysentery and typhoid, tuberculosis, and venereal diseases (including a section on prostitution).

The two decades since 1938 have been very active for the association, and special emphasis is laid on material from this period; this has been arranged, so far as possible, under the principal branches of medicine such as pathology, epidemiology, surgery, and so on. Details of the foundation of the association, membership, organization, amenities, and other matters not directly concerned with clinical medicine occupy about one-third of the book. The section on medical education quotes part of a letter, dated 1809, from one Swedish doctor to another: "... a Dr. Domeyer arrived ... sent by a benevolent society ... to heal and feed the many sick paupers in Sweden! The purpose is pretty good, but the idea in its English way damned silly. For the dear Plumpuddings think that in Sweden there is neither wit nor food nor nursing, and now this one person is to aid us with all this."

Professor Bergstrand has compiled an interesting and readable narrative out of the material at his disposal, and it is clear that his background knowledge has been most valuable.

R. K. Ehrenborg.

MONGOLISM

Le Mongolisme. Principaux Problèmes Médicaux Psychologiques et Sociaux. By Robert Lécuyer. (Pp. 152. 1,500 fr.) Paris: G. Doin et Cie. 1958.

Dr. Robert Lécuyer has written a monograph on mongolism which sets out the facts of this disorder and discusses the medical, psychological, and social problems involved. Like so many French books of this type, it succeeds in conveying an excellent clinical picture without in fact using any illustrations. Also in the French tradition it is paper-backed and without an index. So many details are given with inadequate references (including the usual difficulties with the spelling of English names) that the reviewer is challenged (in the absence of an index) to find omissions. Here only Brushfield's spots can be claimed as a negative finding. The balance is fair, the discussion good, and the author is no partisan for any one theory of causation. In a few years it will be the centenary of Langdon-Down's first description of the mongol. In so far as this calls for any celebration, this book could be counted as a useful contribution to the ceremonies.

Alan Moncrieff.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

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FREEDOM TO GROW

The result of the General Election comes as another reminder to the medical profession that its fate is to a large extent bound up with politics, and party politics at that. No doubt Mr. Bevan is now brushing up his vocabulary in order to deal with a new Conservative Minister of Health. Medical M.P.s, to whom we offer our congratulations on their success, will, we hope, pay as much attention to B.M.A. policy on the Health Service as to the policies of their own and other political parties. The medical profession at large will be excused for thinking of its wage claim, consideration of which cannot now be long delayed as the Royal Commission on Remuneration of Doctors and Dentists in the N.H.S. is reaching its closing stages.

The Royal Commission may propose, but it is the Government that will dispose. If one looks at what the Conservative Government has done in its recent period of office in the way of meeting the just claims of a nationalized profession, the picture is not exactly encouraging. In their Election Baedeker[1] the Tories state that the "Socialist handling of doctors' remuneration was deplorable": Mr. Bevan had assured the medical profession that he accepted the substance of the Spens recommendations, but then did nothing to implement it, "with the result that many doctors were forced by economic pressure to accumulate more patients than they could properly look after." Yet we do not recall that the Conservative Government accepted with jubilation the Danckwerts Award of 1952, which, so far as general practitioners were concerned, went far indeed to implement the Spens recommendations. Their attitude was rather one of "This must never happen again." However, it is to some extent reassuring to notice that in their recent "Campaign Guide" they are interested enough in the Spens Reports to give a concise summary of the effect of these upon remuneration in the Health Service. The Spens Reports may be dying, but they are not yet dead.

It has seemed, and it still seems, that the Conservative Party has not fully grasped the central significance to the medical profession of these reports. And it may be, too, that at times the medical profession has lost sight of this by over-insistence upon this or that detail. There were many things doctors feared would be the outcome of the nationalization of a learned profession that happened in 1948. Among the many things, they feared, and with reason, that they might lose their status in the community and that this would in time discourage the best of the youth of successive generations from taking up medicine as a career. The two Spens Reports provided the two big sections of the profession in the N.H.S. with a charter of living, a guarantee of a certain status within the community.

The Conservative Election Manifesto states that the pay in the Health Service will be considered as soon as the Royal Commission has reported, and adds: "We shall also be ready to consider with representatives of the professions their status in the Health Service." If the new Government puts the two Spens Reports into the discard, then the profession must make absolutely sure that it will secure a new charter that will safeguard its future status, and not be tempted by any immediate monetary advantage to overlook the importance of this.

A year after the introduction of the N.H.S. the Conservative Party[2] said it would strengthen the position of the family doctor "by restoring his freedom to practise anywhere and by offering a weighted capitation fee would give further security to doctors, particularly those in rural areas with small lists." It would be interesting to know whether its views on this remain the same, because in this year's Campaign Guide the Conservatives appear to take credit for the better distribution of general practitioners throughout the country. In 1949 they also stressed the comprehensive nature of the N.H.S. and the fact that "any part of it should be available to any member of the public." They accepted the logical position that private patients should therefore be able "to obtain free of charge drugs prescribed by their doctor on a parity with people in the State scheme." Ten years later the Campaign Guide of 1959 has to admit that private patients are not yet able to do this, though admitting that there is nothing contrary to Conservative principles in the supply of drugs in this way to private patients. In the 1955 Election the Conservatives, expressing belief in the part that could be played by private practice and contributory schemes, stated their determination to retain "the system of hospital amenity and hospital pay beds." And now in 1959 there has been a welcome and reiterated emphasis on the need for new hospital building.

It appears that the new Minister of Science is to be responsible for, among other bodies, the Medical Research Council. The constitution of the M.R.C.

[1] *The Campaign Guide, 1959. The Unique Political Reference Book.* Conservative and Unionist Central Office. 1959.
[2] *The Right Road for Britain.* Conservative and Unionist Central Office. 1949.

has stood the test of time and made it a model for other countries. We hope that the Government will do nothing to affect its independent status or to remove the safeguards against interference built into its constitution by its first Secretary, the late Sir Walter Fletcher.

The next five years are bound to see modifications in the National Health Service. Its virtues and defects after 10 years' experience are now becoming more clearly defined. Much in it is good, and much in it is bad, and the job of the profession in co-operation with the Government is to see that the bad is removed and that the good is made better. The great mistake is to look upon the N.H.S. as something fixed and immutable and the private possession of Mr. Bevan. If the Royal Commission succeeds in finding an acceptable formula for the settling of future remuneration of doctors in the Health Service, then the way will be clearer for co-operation between profession and Government in bringing into being such valuable measures as the Mental Health Bill which was introduced in January this year on the basis of recommendations made by the Royal Commission set up in 1954. The Health Service needs freedom to grow.

AUTO-IMMUNITY AS A CAUSE OF DISEASE

One of the most important observations of the early immunologists was the failure of animals to produce auto-antibodies—that is, antibodies to their own antigens. The first half of the twentieth century contributed little to our understanding of this, and to many students it appeared to be a fundamental and inviolable law of nature. But research into the production of antibody[1] suggested that the body's cells must contain some apparatus to form antibodies which enables the distinction to be drawn between "self" and "not self," and it is presumably the existence of this apparatus that is responsible for the usual failure to form auto-antibodies. Once the existence of such an apparatus is admitted, the possibility of its breakdown must be considered, and indeed the fact of auto-immune disease is now unquestionably established. Its extent and importance, moreover, though at present largely conjectural, are likely to be considerable.

In his Croonian Lectures, reproduced in this and last week's issues of the *Journal*, Sir Macfarlane Burnet draws attention to the inadequacy of classical immunological theory to account for the production of auto-antibodies, and further develops his theory of clonal selection of antibody-producing cells in which auto-antigens have a central role. In contrast to the classical "template" theory, Burnet's concept allows antigen no part in determining specificity of antibody. Instead, he envisages antigen as either stimulating or inhibiting the activity of cells whose immunologically specific products or properties are already genetically determined.

In the absence of precise knowledge of the mechanism by which antigen stimulates the production of antibody, it is well to remember that modification of antigen, as well as of cell clones, may lead to production of auto-antibody. A study of several examples of auto-immune disease throws light on this problem. Thus J. F. Ackroyd's work on purpura caused by apronal ("sedormid")[2] has shown that at least in some cases the combination of a foreign non-antigenic substance or hapten with an endogenous protein may sufficiently modify the latter to render it antigenic. As a consequence, antibodies are formed to the complex, which in this example consists of platelet and apronal. The resultant clumping leads to thrombocytopenia and haemorrhage. The converse, in which the endogenous factor is the hapten and the exogenous factor the protein, has been suggested as the method underlying the relationship between streptococci and such diseases as rheumatic fever and glomerulonephritis.[3] The ease with which non-antigenic substances such as polysaccharides may be converted to full antigenicity by streptococci lends some credence to this hypothesis.[4]

The work of P. B. Medawar and his colleagues[5] on what is usually called specific immune tolerance would illustrate very well Burnet's concept of the "forbidden clone." They have shown that the reactivity of the antibody-forming tissues is largely determined by the antigens present when these tissues are reaching maturity, and in consequence tolerance to a specific antigen can be induced by injecting it some time before production of antibody begins. This varies from species to species but is usually about the time of birth. Presumably tolerance is never acquired to such antigens in the body as lack access to the antibody-forming tissues, and the readiness with which antibodies to thyroglobulin are produced in man may be explicable in this way. Finally, and this may well prove to be the most important of all, auto-antibodies could perhaps arise as a result of some change in the antibody-forming cells themselves, possibly by somatic mutation. In

[1] Burnet, F. M., and Fenner, F., *The Production of Antibodies*, 1949, Melbourne.
[2] Ackroyd, J. F., *Clin. Sci.*, 1949, **7**, 249.
[3] Glynn, L. E., and Holborow, E. J., *Lancet*, 1952, **2**, 449.
[4] —— —— *J. Path. Bact.*, 1952, **64**, 775.
[5] Billingham, R. E., Brent, L., and Medawar, P. B., *Nature (Lond.)*, 1953, **172**, 603.
[6] Kabat, E. A., Wolf, A., and Bezer, A. E., *J. exp. Med.*, 1949, **89**, 395.
[7] Waksman, B. H., and Adams, R. D., ibid., 1955, **102**, 213.
[8] Witebsky, E., and Rose, N. R., *J. Immunol.*, 1956, **76**, 408.
[9] —— —— ibid., 1956, **76**, 417.
[10] Colover, J., and Glynn, L. E., *Immunology*, 1958, **1**, 172.
[11] Freund, J., Thompson, G. E., and Lipton, M. M., *J. exp. Med.*, 1955, **101**, 591.
[12] Frick, E., *Z. Immun.-Forsch.*, 1950, **107**, 411.
[13] Roitt, I. M., Doniach, D., Campbell, P. N., and Hudson, R. V., *Lancet*, 1956, **2**, 820.
[14] Rumke, P., Thesis, University of Amsterdam, 1959.
[15] Glynn L. E., Holborow, E. J., and Johnson, G. D., *Proc. roy. Soc. Med.*, 1957, **50**, 469.
[16] Asherson, G. L, *Brit. J. exp. Path.*, 1959, **40**, 209.

consequence, tolerance might be lost to one or more of the readily available antigens, especially if the postulated homoeostatic mechanism due to inhibition by antigen is also impaired. The auto-antibodies to red-cell antigens found in certain cases of haemolytic anaemia may be due to such a change.

The concept that disease can arise as a consequence of an immune reaction directed against one or more of the antigenic constituents of an individual's own tissues has received considerable support from the results of animal experiments. Lesions in many ways resembling those occurring naturally in man have now been successfully produced in the laboratory in an impressive variety of organs, including the brain,[6] spinal cord and peripheral nerves,[7] the thyroid[8 9] and adrenal glands,[10] the testes,[11] and the kidney.[12] In almost all these experiments use has been made of the adjuvant effect of acid-fast bacilli or of fractions obtained from them. How these adjuvants act to overcome the usual resistance to the development of auto-immune reactions is a major problem, perhaps one of the most urgent problems in this field awaiting solution.

Of the many diseases suspected of arising as a result of auto-immune reactions the evidence is most convincing in the acquired haemolytic anaemias, Hashimoto's disease,[13] and certain cases of male infertility associated with circulating antibodies to spermatozoa.[14] The evidence for a similar pathogenesis of the collagen diseases is less well founded, though in both rheumatoid arthritis and systemic lupus erythematosus serum factors are present which have many of the properties of antibodies against various body antigens—for example, denatured gamma globulin in rheumatoid arthritis[15] and various components of cell nuclei and cytoplasm in S.L.E.[16] But the lack of correlation between the clinical state and the level of these antibodies, both in the natural and experimentally induced diseases, and the failure to enhance the symptoms in any of these conditions by passive transfer of antibodies, have led to the view that they are merely interesting by-products of the disease process. Nevertheless, the discovery of these antibodies in most patients with rheumatoid arthritis and systemic lupus erythematosus has provided a tremendous stimulus to the search for further evidence of auto-immunity as a cause of disease, and it may well be that, as with the tuberculin reaction and other manifestations of delayed hypersensitivity, the active agent is not to be found in the plasma proteins but in the fixed and circulating cells of the lympho-reticular system.

HOW MUCH FLU THIS WINTER?

At this time of year doctors—and potential patients—naturally wonder whether the coming winter will bring an influenza epidemic. On the whole the omens are not too bad. In 1957 we had the pandemic due to a novel strain of influenza A, the A2 or Asian virus. This had its heaviest incidence in Britain in September and October, but about the New Year of 1958 there was an increase in deaths, as there normally is at this season. The increase was attributed to a spread of the A2 influenza at that time to the more vulnerable older people. After the passing of the wave it was found that about 50% of many communities had serological evidence of immunity to the A2 virus. Other serological data had suggested that the Asian virus might represent a recurrence of the pandemic strain of 1889; and prophets arose pointing out that in the early 1890s there were three waves of influenza, each worse than its predecessor. But the influenza virus seems to despise precedents and to invent its own rules as it goes along.

Last winter we seemed to be escaping the evil of a return of A2, though early in 1959 influenza B appeared and caused a moderate outbreak. On the heels of this, however, A2 did reappear, the virus being apparently unchanged from its 1957 make-up. It spread rather widely and caused many deaths, up to a weekly maximum of 1,571 in England and Wales in the week ending February 28. Some accounts indicated a more severe clinical illness than in the 1957 epidemic, but on the whole the virus was not much fiercer. Curiously enough, North America, which had a very similar experience to ours in 1957–8, seems to have had a smaller and patchier outbreak than we did in 1958–9. The same A2 virus was there, but the epidemic seems not to have got up the same momentum. During the last six months A2 has been causing outbreaks in the southern hemisphere—Australia, South Africa, and elsewhere—but there have been no reports of anything extraordinary.

We enter another winter, after outbreaks in two successive years, with populations presumably well over 50% immune and with, as yet, no signs of any further antigenic changes in our new enemy, the A2 virus. Unless such a change occurs, there are no grounds to expect A2 to cause more trouble than last year; it may well cause less. The country had a strong dose of influenza B early in 1959, so it may hope to be fairly free from that; and we are at a loss to discover the basis for alarmist prophecies recently appearing in the lay press.

[1] *Brit. med. J.*, 1958, **2**, 732.

The advice that may be given about vaccines is much as it was last year. They are available and have a likelihood of reducing the incidence of the disease by about two-thirds. The immunity they confer cannot be expected to last more than a year, so that they must be administered annually to be effective against that winter's outbreak. They are best given in November or early December. Monovalent Asian (A2) vaccines are to be preferred to polyvalent vaccines, which often have their useful components diluted by unwanted ones. Moreover, unwanted antigen can partly divert the antibody-producing mechanism from making those antibodies needed to combat the epidemic strain of virus, and the injection of too much antigenic substance can be toxic. A good compromise might be a bivalent vaccine containing A2 and B components. But, as we said last year,[1] the question whether to be inoculated is "a matter for personal choice rather than for a country-wide campaign."

TRANSFUSION REACTIONS

Despite reasonable care, unpleasant reactions still occur after blood transfusion. Some, such as pyrogen and allergic reactions, are not serious, but others, such as citrate[2] and potassium[3] intoxication, transmission of disease such as viral hepatitis,[4] development of a generalized bleeding state[5] or of acute renal failure may be so severe as to lead to death. Transfusion of incompatible blood is the main cause of trouble, and it is difficult to assess the incidence of this mishap. A recognized haemolytic reaction occurs on the average once in about 3,000 transfusions, and an estimate of one death per 13,000 bottles of transfused blood has been reported.[6] If the numbers of the reported cases of acute renal failure after transfusion are taken as an index, the hazards of transfusion would seem to be unusually high in some countries.[7 8] But this index is misleading, because the condition for which the transfusion is given—for example, post-partum haemorrhage—may alone be responsible for the development of acute tubular necrosis. Indeed, it is doubtful whether the excretion of haemoglobin by a normal kidney causes renal damage, though intravascular haemolysis may cause renal vasoconstriction and oliguria.[9]

Writing on transfusion reactions and their treatment, especially with the artificial kidney, G. M. Barlas and W. J. Kolff[10] report 16 patients admitted to the Department of Artificial Organs in Cleveland, Ohio, between 1954 and 1958 for treatment of renal failure. They imply that transfusion of incompatible blood caused the development of the renal failure in all cases, but the critical reader might welcome more detailed case histories before feeling certain of this. The authors consider three phases in such cases—the acute phase, the oliguric phase, and the diuretic phase—and draw attention to the masking effect of general anaesthesia on the clinical features of the acute phase. If shivering, fever, pains in the loins, headache, nausea, vomiting, collapse, hypotension, or undue bleeding occur during a transfusion, they recommend immediate cessation of the transfusion, withdrawal of a blood sample from the patient for evidence of haemolysis and for direct cross-matching with blood from the suspected bottle, administration of 2 l. of 5% dextrose with 300 mEq of sodium bicarbonate, and, when indicated, blood proved to be compatible or dextran. This treatment is similar to that recommended in Great Britain.[11] With development of the oliguric phase—and this is unlikely to occur in more than 10% of cases[12]—treatment closely follows the principles evolved by G. M. Bull and his colleagues.[13] This consists nowadays chiefly in fluid restriction, administration of carbohydrate, and, on occasion, the use of ion-exchange resins.[14] The place of prophylactic antibiotics is doubtful. In any case, erythromycin alone is better avoided and a combination of chloramphenicol and tetracycline is to be preferred.

Barlas and Kolff used the twin-coil disposable artificial kidney when their conservative methods seemed inadequate to control the clinical and biochemical deterioration which precede spontaneous adequate diuresis. Twelve patients were treated by dialysis while the remaining four recovered after conservative management alone. Three of the dialysed patients died. Barlas and Kolff conclude that the treatment of a patient who has received an incompatible transfusion is best given at a centre where facilities exist for dialysis. This may be so, but if an artificial kidney is not readily available no time should be lost before starting treatment on the usual lines.

FROG BREATHING

It is possible for a patient to breathe without using either the primary or the ordinary accessory muscles of respiration. Patients in different parts of the world, paralysed by poliomyelitis, have independently made this discovery. C. W. Dail, in the U.S.A., was first to recognize its importance and to teach other patients the technique.

The method is known as frog breathing or glosso-pharyngeal breathing (G.P.B.). It has been described crudely as a process of "swallowing" air rapidly into the lungs. Dail and his colleagues[1] described four steps. In the first the tongue is depressed and the pharynx is widened so that the mouth and pharynx contain a considerable amount of air. In the second the lips are closed and the soft palate is raised so that the air cannot escape to the exterior. In the third the floor of the

[2] Bunker, J. P., Stetson, J. B., Coe, R. C., Grillo, H. C., and Murphy, A. J., *J. Amer. med. Ass.*, 1955, **157**, 1361.
[3] Stewart, H. J., Shepard, E. M., Horger, E. L., *Amer. J. Med.*, 1948, **5**, 821.
[4] Neefe, J. R., Norris, R. F., Reinhold, J. G., Mitchell, C. B., and Howell, D. S., ibid., 1954, **154**, 1066.
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[6] Binder, L. S., Ginsberg, V., and Harmel, M. H., *Surg. Gynec. Obstet.*, 1959, **108**, 19.
[7] Hamburger, J., Richet, G., Funck-Brentano, J. L., Ducrot, H., Antoine, B., and Crosnier, J., *Rev. Méd. Liège*, 1958, **13**, 74.
[8] Salisbury, P. F., *Arch. intern. Med.*, 1958, **101**, 690.
[9] Blackburn, C. R. B., Hensley, W. J., Kerr Grant, D., and Wright, F. B., *J. clin. Invest.*, 1954, **33**, 825.
[10] Barlas, G. M., and Kolff, W. J., *J. Amer. med. Ass.*, 1959, **169**, 1969.
[11] Mollison, P. L., *Blood Transfusion in Clinical Medicine*, 1956, Oxford.
[12] Discombe, G., *Blood Transfusion*, 1955, London.
[13] Bull, G. M., Jockes, A. M., and Lowe, K. G., *Lancet*, 1949, **2**, 229.
[14] Parsons, F. M., and McCracken, B. H., *Brit. med. J.*, 1959, **1**, 740.

mouth is raised so that the tongue almost fills the cavity of the mouth, the pharynx is constricted, and the larynx opened. The air from the mouth and pharynx is forced through the larynx into the chest. Finally, the larynx is closed, trapping air in the chest and bronchial tree, and the cycle begins again. Each cycle, or gulp, introduces some 40–50 ml. of air into the lungs, and gulps are repeated rapidly so that many hundreds of millilitres of air enter the chest before the patient opens his larynx and mouth simultaneously and breathes out. G. M. Ardran and his colleagues[2] have recently studied G.P.B. by cineradiography, and, while confirming Dail's description in general, have detected a number of variations in technique adopted by different patients.

The great value of G.P.B. for patients with severe respiratory weakness is obvious. It enables patients whose vital capacity without G.P.B. is only a few hundred millilitres to be without artificial respiration for many or all of their waking hours. It gives them the extra ventilation necessary for travelling by car or otherwise, and it gives them confidence to leave artificial aid behind when they go out for the day. Moreover, they are much safer when they get the inevitable chest infection, for with the added vital capacity they can produce a cough adequate to remove secretions from their chest. Patients who rely largely on G.P.B. when awake require artificial respiration when asleep, because G.P.B. is a conscious activity. Again, artificial respiration is often required during meals. Normal subjects occasionally use G.P.B. to add to their vital capacity when swimming under water, but this is an undesirable practice, because the raised intrathoracic pressure combined with breath-holding may cause unconsciousness.

Some patients find G.P.B. easy to learn, others remain incapable after months of instruction. It is apparently easier to learn if some normal vital capacity exists; and, though a tracheotomy does not prevent G.P.B., it complicates it. For the patient with an appreciable vital capacity instruction in G.P.B. is essential. But a difficult choice has to be made if the patient has no normal vital capacity at all. Many patients who are so severely affected by poliomyelitis that their respiratory muscles are completely and permanently paralysed have required a tracheotomy in the acute stage, and receive artificial respiration through it by intermittent positive pressure.[3] The respirators required for this type of artificial respiration are portable, and such patients can readily be taken out in a wheel-chair or motor-car.[4] Indeed, one such patient, almost totally paralysed below the neck, took part in the *Daily Mail* race from the Marble Arch to the Arc de Triomphe. If such patients can with certainty be taught G.P.B. well enough to permit them to breathe unassisted for most of their waking hours, then it may be wise to close the tracheotomy and concentrate on teaching G.P.B.; but if they do not become expert at G.P.B. their state is made worse by closing the tracheotomy, for they are then confined to a tank respirator and thereby immobilized. Then minor respiratory infection becomes a serious risk. At present it seems wise not to attempt the closure of the tracheotomy in patients with complete respiratory paralysis unless they are first capable of useful G.P.B.

[1] Dail, C. W., Affeldt, J. E., and Collier, C. R., *J. Amer. med. Ass.*, 1955, **158**, 445.
[2] Ardran, G. M., Kelleher, W. H., and Kemp, F. H., *Brit. J. Radiol.*, 1959, **32**, 322.
[3] Walley, R. V., *Brit. med. J.*, 1959, **2**, 82.
[4] Sutcliffe, R. L. G., and Spalding, J. M. K., *Lancet*, 1959, **1**, 706.

A VACCINE TREATMENT OF CANCER

An interesting therapeutic experiment has recently been reported in the U.S.A.[1] in which patients with cancer of various types have been inoculated with a vaccine prepared from their own tumours. The theory behind this is that the tumour may contain substances which will evoke an antibody response in the patient provided they are given a helping hand. In earlier work these authors, J. B. Graham and Ruth M. Graham, had found antibodies against tumours in the blood of some patients with cancer of the breast.[2] Their present work follows on from that.

In order to give the hypothetical antigens of the tumour every chance to immunize the patient, Graham and Graham tried various cell fractions of the tumour, and incorporated the preparations in Freund's adjuvant before injection.[3] This substance has proved a great boon in immunology. It consists of a light mineral oil to which killed tubercle bacilli and an emulsifying agent have been added. The antigen is mixed with this in such a way as to give a stable water-in-oil emulsion. Such preparations have been shown to have an immunizing power twenty times or more that of the antigen given by itself.

Armed with these vaccines Graham and Graham treated 114 cases of advanced cancer, mainly of the female genital organs. Four types of tumour-cell preparation were employed: a whole-tumour homogenate, a one-molar sodium-chloride extract of tumour (containing the desoxyribonucleoprotein), a normal-saline extract, and finally a whole-cell suspension. The results obtained are difficult to assess, because the experiment was not designed to permit statistical analysis. The best results suggest that the vaccine might have an effect in some patients. Thus, in six cases in which extensive tumour was removed but the surgeon had doubts about the completeness of removal, there were five patients clinically free of the disease seven months or more after the vaccine and no other treatment. Of 29 patients in whom cancer was left after partial excision and who had received vaccine, there were two in whom no tumour could be detected. There was also a suggestion that the vaccine might have improved the effect of later radiotherapy. It is interesting that the best results were obtained when the vaccine contained either whole tumour cells or whole-cell homogenate. This suggests that the antigen, if it exists, may be on the cell membrane. However, the experiment must be regarded as preliminary and judgment suspended until better-controlled experiments are reported.

[1] Graham, J. B., and Graham, R. M., *Surg. Gynec. Obstet.*, 1959, **109**, 131.
[2] —— —— *Cancer (Philad.)*, 1955, **8**, 409.
[3] Freund, J., and Bonanto, M. V., *J. Immunol.*, 1944, **48**, 325.
[4] —— Thompson, G. E., and Lipton, M. M., *J. exp. Med.*, 1955, **101**, 591.

The main interest of the work is that it appears to be the first time this technique has been attempted in man on such a scale. If nothing else comes out of it the mere discovery that such vaccines can be administered without serious complications is a valuable piece of knowledge. More subtle vaccines can be expected in the future as the cell becomes better explored. Meantime the authors deserve credit for not being put off by the negative results that have been obtained with animal tumours. As they rightly point out, tumours in laboratory animals grow so fast that they may not be comparable with human tumours in regard to the process of immunization.

PSYCHOCHEMICAL WAR

After poison gas, and bacteriological and radiological warfare, comes the chemical attack on the mind. At recent hearings[1] of an American Congressional Committee on Science and Astronautics, spokesmen for the U.S. Army Chemical Corps reported on chemicals which would cause sensory disturbances (of hearing, vision, and balance), Parkinsonism, or mental derangement, lasting a day or two but without permanent ill-effects. Troops and civilians could be temporarily incapacitated by these substances delivered as gas clouds or aerosol mists from bombs or the warheads of rockets, so allowing the troops of the other side to advance unresisted. It was suggested that this might be a humane sort of warfare, since no one need be killed or permanently injured.

Two groups of chemicals were mentioned. The nerve gases, developed and well studied in the last war, are organophosphorus compounds which inhibit cholinesterase irreversibly: some of them have found peacetime use as insecticides, and one, D.F.P. or di-isopropylfluorophosphate, has had quite extensive trial in medicine as treatment for myasthenia gravis and glaucoma. Some observations on the effects of accidental exposure to nerve gas have recently been published.[2] The hallucinogens represented by lysergic acid diethylamide (L.S.D.-25) and its relatives have been much used in the past fifteen years to produce artificial psychoses in volunteers in the hopes of throwing light on the nature of schizophrenia and its medical treatment. Visual hallucinations, misinterpretations, preoccupation with inconsequential detail, disturbance of thought processes, are among the frequently described symptoms of L.S.D.-25 intoxication after absorption of microgramme doses.[3]

There are of course a great many substances which can interfere with mental processes, from alcohol, amphetamine, and atropine onwards, through reserpine and the phenothiazines and iproniazid.[4] Chemical and pharmaceutical firms are discovering new ones all the time. Very few, however, are suitable for military use. Obviously they must be convenient to manufacture and store in bulk; they have to be delivered in some kind of shell or spray; and, like other agents of chemical warfare, they are subject to all the capricious variations of wind and weather which reduce their effectiveness. Gas-masks and protective clothing can nullify the attack, and pharmacological antidotes often exist, but detection may be a difficult problem. The principles of this kind of warfare are, however, no different from chemical warfare in general: the target in the past has been the lungs or the skin or the bone marrow, now it is the brain.

The U.S. Chemical Corps gets about £10m. a year for research and development and wants a rise to £40m. to expand its psychochemical work. Ironically it is already allocated more than three times the funds granted to the Medical Research Council in Britain for research in the whole field of medicine (of which psychiatric research gets about 1%). Research on natural mental illness lacks the urgent appeal of the science of defence and attack, and consequently little money is spent on it. Yet perhaps some fraction of the millions spent and the work done on psychochemical warfare will provide new understanding of brain function and new treatment for mental illness.

[1] *Hearings Before the Committee on Science and Astronautics U.S. House of Representatives.* Eighty-Sixth Congress, First Session, June 16 and 22, 1959, U.S. Government Printing Office, Washington.
[2] Craig, A. B., and Woodson, G. S., *Amer. J. med. Sci.*, 1959, **238**, 13.
[3] Wikler, A., *The Relation of Psychiatry to Pharmacology*, 1957, Baltimore.
[4] de Boor, Wolfgang, *Pharmakologie und Psychopathologie*, 1956, Berlin.

BARBITURATE DEATHS INCREASING

The numbers of people dying in England and Wales each year from poisoning, whether accidental or suicidal, have greatly increased in the last few years. In 1949, for instance, there were 80 deaths from accidental poisoning by morphine and barbiturates; in 1957 (the latest year for which figures are available) the total was 210.[1] Likewise for suicide by analgesic and soporific drugs: in 1949 there were 355 deaths, while in 1957 there were 695. The greater resort to drugs to commit suicide is not in proportion to the increased number of suicides, which has been slight in comparison, for in 1947 the number of suicides by these drugs comprised 7.5% of all suicides, whereas in 1957 they comprised 13%.

When all causes of suicidal poisoning are considered, it is evident that deaths due to drugs greatly outnumber those due to household and industrial poisons. Detailed figures provided by the Registrar-General for 1957 have recently been published,[2] and they show, as might be expected, that barbiturates are the most prominent group of drugs causing these deaths. Out of 695 suicidal deaths due to drugs they caused about 75%. In the remaining 25% the chief offender was aspirin, causing about 20% of the total. As to accidental deaths from all types of poisoning, barbiturates are again the most important group, causing 208 out of 253, or about 80%.

Probably most of the people who commit suicide with these drugs are under their doctor's care, and so, fairly often, are those whose death from them is an accident. The difficulties of preventing patients helping themselves to an overdose are evident, and the usual practice is to prescribe only small quantities when the doctor considers the situation merits special care. But the increasing number of these deaths would suggest that something more is needed.

[1] *Registrar-General's Statistical Review of England and Wales for the Year 1957*, Pt. 1, Tables, Medical. 1958. H.M.S.O.
[2] *Pharm. J.*, 1959, **183**, 180.

NEW ACADEMIC YEAR

ROYAL FREE HOSPITAL

"Nothing in our specialized studies can justify denying ourselves the right—and indeed the intense pleasure—of writing and speaking our language well or continuous access to the refreshing treasures of our great writers," Dr. JOHN LOCKWOOD, Master of Birkbeck College, told students of the Royal Free Hospital School of Medicine in his inaugural address on October 2. Were he to ask what books, apart from the large volumes to which medicine seemed to run, students had read, would he find, for example, Shakespeare, Smollett or Jane Austen, Burke or Macaulay, Bacon, Hazlitt or Lamb? Or King James's Bible? And yet it was from such reading that true feeling for language came.

Credit will be Given for Good English

There never had been a language so fitted for almost all the needs of speech and writing as English. In the course of his survey of its use in different forms the Master of Birkbeck remarked: "How I wish that rhetoric in the classical sense were still part of the curriculum of our schools! We should not then have been driven to add a rubric to the G.C.E. papers of our University: 'Credit will be given for good English.' What a reflection on our age of scholarship and learning!"

The prime function of language was to communicate thought or feeling intelligibly; and for most needs simple, concise, lucid, logical expression was enough. "But go to the meeting of a committee and what do you hear? Often raw slices of maundering, repetitive, ungrammatical, formless jargon. Look at the agenda of many academic committees, at the letters and documents which pour in upon one from departments of Government, from advertisers, from candidates. Diffuse, tedious, and turgid. Too many people will not take the trouble to keep to a brief, terse, controlled style and to cut out the unnecessary and falsely impressive.

"When you come to give instruction for treatment, you will have to look to choice and arrangement of words," concluded Dr. Lockwood. "On the clarity of your words may hang at the worst a life, at the best a speedy or complete recovery."

The dean, Dr. KATHARINE LLOYD-WILLIAMS, presenting her report for the 1958–9 session, said that a most important decision about the future was made during the current year when the University of London succeeded in convincing the University Grants Committee that the pre-medical and preclinical departments should be rebuilt on the same site as the new hospital at Hampstead. This, which seemed so obvious, was by no means accepted without argument by the University Grants Committee. Every recent development in medicine had emphasized the need for the closest integration between clinical and pre-clinical departments, and with the prospect of the Royal Free being rebuilt, starting in 1961, there was opportunity to replan with this object in mind. There was no special grant for the new building, and it might well be that the School would have to make efforts to raise funds.

WESTMINSTER HOSPITAL

Adapting the school and university curriculum to meet the challenge of the years that lie ahead was the subject of the inaugural address delivered by LORD JAMES OF RUSHOLME, High Master of Manchester Grammar School, to Westminster Medical School on October 5.

Medicine and General Education

Medicine bridged the gap between science and the arts, and medical education, which partook of both, raised interesting questions concerning the content of the curriculum for students who had to be scientists on the one hand and humanists on the other. In Dr. Arnold's day Latin, Greek, and Ancient History filled the curriculum. With the increasing speed of travel and the growth of scientific knowledge, modern languages and history had been added, while practically every school now taught science. Even quite good schools had begun to teach English and geography. Compulsory games were thought essential to the development of certain attributes of character, and, if pupils had minds and bodies, they also had what might be called "spirit," and no school could fail to provide some kind of emotional education. Constant pressure for the inclusion of still more subjects led to schools and universities becoming battlegrounds of competing interests. Lord James said he would like to go down to posterity as the inventor of a law which stated that for every subject introduced into the curriculum something else must be taken out.

As a result of the growth of science, young men had to know far more than their predecessors, and this led to increasing specialization. Grammar schools were faced with the problem of mitigating this specialization if they were to produce future chemists, doctors, or physicists with a sound appreciation of the humanities. One way would be to continue the humanistic education in science, another to continue the scientific education of the arts student—but at present there were insufficient scientists to teach even the science students. He did not personally believe that the much discussed gulf between the humanists and scientists existed any longer. Scientists were as sensitive to pictures, music, and literature as most of their contemporaries, but there was a problem of interest and ability, and not every graduate could be expected to discuss Proust.

Higher education was available to students from a wider cultural background than ever before, and this placed a heavy responsibility on schools to provide a genuine education which would produce young men and women who had been given some glimpse of the classical tradition and culture. This aim could not be achieved by following the practice at Oxford and Cambridge of forcing science entrants to pass an examination in ordinary-level Latin: there was a great gap between this standard and appreciating the "surge and thunder of the Odyssey."

In both schools and universities leisure had to be rediscovered, so that by broadening the curriculum the days were not entirely taken up with general education, games, and examinations, to the exclusion of reading, thinking, and talking, which in the long run were the only educational activities that mattered. A great effort of co-operation between schools and universities would, he said, be required if the problems were to be solved.

The French National Institute of Statistics has recently published figures showing that deaths from alcoholism in France dropped from 14 per 100,000 inhabitants in 1956 to 10 per 100,000 in 1958. Deaths from cirrhosis of the liver fell during the same period from 33 to 26 per 100,000. A contributory factor may be the energetic propaganda campaign started by M. Mendès-France in 1954, with the aim of reducing drinking in France to within reasonable limits. At least 70% of the alcoholism there is due to wine-drinking; doctors suggested, and posters exhorted, that a litre (1¾ pints) a day was the most that a manual worker should drink, three-quarters for a sedentary worker, half for a woman, a watered quarter for adolescents, and none at all for children under 14 (the compulsory distribution of unwatered wine to children at school meals has only recently been stopped). At this rate only 456 million litres of wine would be drunk a year, as against the 650 millions drunk in 1958. A French researcher has estimated that 20% of French adults drink 1 to 2 litres of wine a day, and 7% more than 2 litres. So four and a half million Frenchmen drink more than they should, and nearly 2 million are in what the French language elegantly calls "un état d'imprégnation éthylique grave." The propaganda campaign, particularly if allied to a constructive policy for viniculture designed to avoid disrupting the French economy, should reduce deaths and disorders due to alcohol even further.

Nova et Vetera

THE EARLY DEVELOPMENT OF GALL-BLADDER SURGERY

CENTENNIAL OF THE PROPOSED CHOLECYSTOSTOMY OF J. L. W. THUDICHUM

BY

ROBERT S. SPARKMAN, M.D., F.A.C.S.

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One hundred years ago, on October 17, 1859, Dr. J. L. W. Thudichum addressed the Medical Society of London on the subject of "The Pathology and Treatment of Gall-stones." On this occasion Thudichum proposed, for the first time, elective operation in appropriate cases of gall-stone disease.

A brief review of this meeting appeared five days later in the *Lancet*.[11] The complete text of Thudichum's presentation was published the following month in the *British Medical Journal* for November 19, 1859.[12] The procedure which he suggested was as follows:

"In decided cases of gall-stones in the bladder, where continuous symptoms or repeated passages of concrements are observed, the surgeons should consider the propriety of planning and performing an operation for the extraction of these foreign bodies, either in a direct manner, or by forming a biliary fistula and adopting a lithotriptic proceeding. The operation is much slighter than lithotomy. Compared to such operations upon the abdominal cavity as extirpation of ovarian tumours, it sinks into insignificance. If, for example, an incision was made a little above the lower edge of the liver, just large enough to admit the forefinger into the peritoneal cavity, the gall-bladder might be explored, and the presence or absence of calculi determined with the greatest certainty and the least danger. If calculi are present, the gall-bladder is seized with a small hook, pulled into the abdominal wound, and fixed there without being opened. In six days a good and passable fistula will be established, which, after a fortnight or three weeks, will be sufficiently consolidated to admit of the introduction of an instrument, by which such soft calculi may easily be crushed. The calculi once removed, I make no manner of doubt that the fistula would heal up by itself. I am certain that, with proper care and dexterity, surgeons might make a number of these operations successful, and have few failures; considering always that cases suitable for the operation would perhaps be half as common as cases for lithotomy."

Prior to the time of this presentation, and indeed for several years thereafter, operations upon the gall-bladder were confined to those instances in which rupture of this organ had led to the development of an external fistula or an abscess of the abdominal wall. Such operations usually consisted of drainage of abscesses, enlargement of cutaneous fistulas, or withdrawal of calculi through them. While Petit[8] appears to have been the first to perform an operation upon the gall-bladder, his cases were limited to those instances in which such complications had developed.

Early Operations

Thudichum's proposal attracted little attention. Eight years were to elapse before the performance of the first operation upon the gall-bladder. On June 15, 1867, John Stough Bobbs,[1] of Indianapolis, Indiana, operated upon a woman thought to have an ovarian tumour. The mass proved to be a huge hydropic gall-bladder. Many stones and much fluid were removed, and the opening in the gall-bladder was closed. The patient survived, and was able to attend a meeting of the American Medical Association 37 years later. There is no indication that Bobbs was aware of the suggestion which Thudichum had made.

The first premeditated operation upon the gall-bladder was performed by J. Marion Sims on April 18, 1878, and was reported in detail in the *British Medical Journal*.[9] The patient, a woman, had been deeply jaundiced for five months. Sims opened the distended gall-bladder, removed some 60 stones, and sutured the opened gall-bladder into the wound. Eight days after operation the patient died of haemorrhage presumably resulting from prothrombin deficiency. Nowhere in his report did Sims mention Thudichum, although he did state that operation for impacted gall-stones had been suggested by Handfield Jones.[3]

The third operation upon the gall-bladder is credited to Theodor Kocher,[5] of Berne. This operation, a two-stage cholecystostomy, was performed in a manner quite similar to that which had been suggested by Thudichum. On June 18, 1878, Kocher operated upon a woman of 30 thought to have an ovarian cyst. At operation a distended gall-bladder was discovered. A piece of "Lister-gauze" was placed over the gall-bladder and the margins of the wound were packed apart. Seven days later the wall of the gall-bladder was incised and stones were removed. The patient subsequently recovered. Nineteen years had elapsed from the time of Thudichum's proposed operation until its actual performance. Thudichum was not mentioned in Kocher's report.

The fourth operation upon the gall-bladder was performed by W. W. Keen,[4] of Philadelphia, on November 4, 1878. The patient, a female 60 years of age, had been deeply jaundiced for four months; a mass in the right upper abdomen was correctly interpreted to represent a distended gall-bladder. This was the second premeditated operation upon the gall-bladder. The opened gall-bladder was sutured to the abdominal wall. As in Sims's case, the patient died of haemorrhage, presumably due to faulty coagulation. Keen stated that the operation performed by him had originally been proposed by Petit and later by Maunder and Hughlings Jackson, but did not mention Thudichum. He was not aware of the previous performance of such an operation by anyone except Sims, and stated that, to the best of his knowledge, this was only the second case in which cholecystostomy had been accomplished.

The fifth recorded operation upon the gall-bladder was performed by Mr. Lawson Tait, and was reported to the Royal Medical and Chirurgical Society on November 11, 1879. The proceedings of this session of the Society were published in the *Lancet* for November 15, 1879.[10] The patient, an adult female, had been aware of a tender mass in the right upper abdomen for eleven months. At operation on August 23 a distended hydropic gall-bladder was disclosed; the obstructing cystic-duct stone was removed and the opening in the gall-bladder sutured into the wound, "leaving the aperture into the gall-bladder quite open."

The patient recovered. In an enlightening discussion which followed Mr. Tait's presentation, a Mr. Hulke pointed out that the credit for advocating such a procedure was generally accorded in Great Britain to Dr. Handfield Jones, but that in 1743 Petit had published an admirable memoir on this very subject and with the same intent. A Mr. Morris confirmed Mr. Hulke's remarks, and added that Dr. Thudichum had suggested the same operation at a meeting of the Medical Society in 1859. On this occasion, for the first time, Thudichum received a measure of credit for his original proposal, first recorded in the same journal 20 years before. In his closing remarks following the above discussion, Mr. Tait stated that Mr. Hulke's remarks showed how careful one should be in bibliographical research, and confessed that he had gathered his knowledge of the history of the operation from Dr. Sims's paper, where priority for the idea was given to Handfield Jones.

The first cholecystectomy was performed by Carl Langenbuch,[6] of Berlin, on July 15, 1882. This is the sixth recorded operation upon the gall-bladder in the modern era. The patient recovered. While Langenbuch made no comment concerning priority for the concept of elective surgery upon the gall-bladder, he did state that "the surgery of the gall-bladder is still in the beginning of development, but it exists, and the names Petit, Thudichum, M. Sims, Kocher, G. Brown, Lawson Tait, Koenig *et al.*, are connected with it in a prominent way."

In the first comprehensive review of surgery of the gall-bladder, published in 1884, Musser and Keen,[7] of Philadelphia, collected from the literature 31 instances in which operations had been performed upon the gall-bladder. In discussing the operation of cholecystotomy (later to be called cholecystostomy) they remarked that "the first one to propose this operation was undoubtedly Thudichum, in a paper on the 'Pathology and Treatment of Gallstones.'" Twenty-five years had elapsed until this categorical acknowledgment of Thudichum's priority was finally made.

Thudichum on Gall-stones

Having once proposed operation upon the gall-bladder, Thudichum apparently refrained from any mention of this subject thereafter. Four years later, however, in a text entitled "A Treatise on Gall-stones: —Their Chemistry, Pathology, and Treatment,"[13] he propounded the nidus theory for the formation of biliary calculi. A most favourable review of this work appeared in the *British Medical Journal* for March 7, 1863.[14] The writer stated that "in constructing as a chemist a theory of the formation of these bodies which bears a strong aspect of probability, and in furnishing at the same time the results of his observations as a practical physician, he has made a valuable contribution to scientific medicine." The introductory historical survey of this book is considered a classic, and is acknowledged by the reviewer as follows: "The book consists of six chapters. In the first, the author gives a Digest of the Historical Literature of Gall-Stones; referring to all who have described or written on them from Alexander Trallianus down to Frerichs. This chapter is apparently most complete, and must have cost the author much searching among old books." Thudichum also made discoveries of fundamental importance concerning the chemistry of the bile pigments.

A Versatile Pioneer

From the foregoing, a reader heretofore unacquainted with Thudichum and his career would presume that this man devoted the bulk of his investigative effort to the biliary tract. On the contrary, his publications numbered over 200, and covered a phenomenal range of subject material. His monumental contribution was achieved in the study of the chemistry of the brain, to which he devoted his major investigative effort. He was, moreover, the discoverer of the carotenoid pigments, the precursors of vitamin A, and of various pigments of blood and urine. Despite his extensive programme of biochemical investigation, he became the leading otolaryngologist of his day, noted for his operations on nasal polyps and for the invention of a nasal speculum which is still in use. He was a pioneer in public health and industrial medicine. He wrote authoritative works on the chemistry of wine and beer, and published a large cookery book. These and other details of his fascinating career are to be found in a recent biography, *Thudichum. Chemist of the Brain*, written by Dr. David Drabkin,[2] of Philadelphia, and published in 1958.

In a detailed and sympathetic account of the fascinating career of Thudichum, Drabkin portrays not only the genius of the man and the vast scope of his accomplishments, but also the disappointments, rebukes, and controversies which he encountered throughout his career. His greatest work was discredited by his contemporaries, and within 25 years after his death his name was all but forgotten. Proof of the validity of his work on the chemistry of the brain was finally established in 1930 by the noted British biochemist Otto Rosenheim. The story of Rosenheim's posthumous discovery and analysis of Thudichum's preserved specimens is one of the high points in the Drabkin biography.

In Galesburg, Illinois, at the State Research Hospital for the mentally ill, a psychiatric research laboratory was dedicated in 1953 as the Thudichum Laboratory and the annual Thudichum Lectures were initiated. On the whole, however, recognition of Thudichum and his accomplishments has come slowly, and few contemporary surgeons are even aware of him. The history of modern gall-bladder surgery may be said to have begun 100 years ago with the proposed cholecystostomy of Thudichum. Our indebtedness to him is hereby acknowledged.

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Dr. S. G. Browne, who until earlier this year was a missionary of the Baptist Society and medical superintendent of the Yakusu Hospital and Talisombo Leprosarium in the Belgian Congo, has been awarded the distinction of "Officier de l'Ordre de Leopold II" by King Baudouin. Dr. Browne was made "Chevalier de l'Ordre Royal du Lion" some years ago.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Sparine (Wyeth).—This is promazine hydrochloride, (Fig. 1), a phenothiazine derivative differing in chemical structure from chlorpromazine (Fig. 2) by the absence of a chlorine atom.

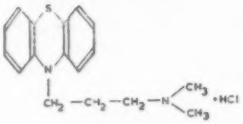

FIG. 1

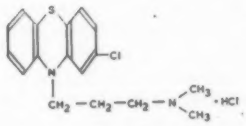

FIG. 2

In animals promazine is less sedative, less toxic, and causes the following effects in the body less strongly than chlorpromazine: hypotension, anti-emesis, potentiation of narcotics, mydriasis, reduction of temperature, and blocking of conditioned reflexes. It has a greater antihistamine action than chlorpromazine and greatly reduces aggressiveness in animals.

Clinical Effects.—Promazine gives powerful sedation without causing unconsciousness, so that the subject can be roused to eat and to co-operate. This is useful when treating patients in such states of excitement and inanition as acute alcoholic intoxication or delirium tremens, and the withdrawal stage in treatment of drug addiction. 100–400 mg. daily, divided in three or four doses, is the usual dosage required, starting low and increasing until the required calming is produced. The lack of irritation after intramuscular injection is an advantage. Promazine has also been found helpful in treating restless old people. Daily doses of 400–1,000 mg. have been given over periods of several months to chronic schizophrenics, with a considerable reduction in dose when an improvement has been obtained; but these patients usually do distinctly better on chlorpromazine. There is no evidence that it is of benefit in depression or neurosis.

Contraindications.—Promazine should not be given to patients under the influence of narcotics or when the leucocyte count is low.

Side-effects.—These have been fewer than with chlorpromazine. In particular jaundice has not been reported and laboratory tests show no evidence of liver damage. Drowsiness and dizziness occur frequently, postural hypotensive effects and Parkinsonism infrequently. Epileptic fits are provoked more often than with any other phenothiazine. Fatal agranulocytosis has been reported.

N.H.S. Basic Price.—250 tabs. of 25 mg., 27s. 9d.; of 50 mg., 52s. 4d.; of 100 mg., 102s. 6d.; amps., 10 × 2 ml.,

Hexopal (Bayer).—This is meso-inositol hexanicotinate, and is an ester of nicotinic acid. It has been introduced for the treatment of peripheral circulatory disorders. Nicotinic acid has a limited effectiveness in the treatment of these conditions, and hexopal is a closely related substance with a similar action. Little clinical work has yet been published on it, but the impression gained in small groups of patients has been that it causes fewer side-effects than some similar preparations. Like many other drugs, it has been suggested for trial in the treatment of migraine.

Hexopal is supplied in 200-mg. tablets, and an initial dosage of two tablets three times a day is recommended, which may be increased up to 16 or 20 tablets a day according to the response. The treatment may need to be continued for two to four weeks for maximum effect.

N.H.S. Basic Price.—40 tabs. for 7s. 10d.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

R.M.B.F. Christmas Gifts Fund

SIR,—I shall be very grateful if you will spare space for me to remind your readers that Christmas will be coming round again soon, and to ask them to give a kind thought and a generous gift to the Christmas Gifts Fund organized by the Royal Medical Benevolent Fund.

To receive a gift at Christmas-time is a joy to everyone, but particularly to those who are lonely or in need. To none is a gift more welcome than to those who have fallen on hard times.

Our beneficiaries include colleagues who have met with misfortune, and widows and children who are often in desperate need when their breadwinner has been taken before he was able to make provision for them. A gift at Christmas will enable them to enjoy some of the traditional good cheer of the season. I ask your readers once again to give generously. Contributions, marked "Christmas Gifts," should be sent to the Royal Medical Benevolent Fund, 37, St. George's Road, Wimbledon, London, S.W.19.—I am, etc.,

HENRY TIDY,
President,
Royal Medical Benevolent Fund.

London, S.W.19

"Lipostabil"

SIR,—I have read with interest the paper on "lipostabil" by Dr. L. G. G. Davies and Miss Lesley Murdoch (*Journal*, October 3, p. 619). I think their conclusions should be treated with considerable reserve.

At this hospital we have now examined the effect of this substance on blood proteins and lipids for periods up to one year and in 50 subjects to date. I have recently analysed our findings and still feel that further study is necessary before any firm conclusions should be drawn from them, although we have already about 2,500 biochemical results. This is because, firstly, the lipids are themselves changing at the time of infarction, and, secondly, the German physicians claim that blood changes in response to lipostabil are different some months after infarction from what they are in the recovery period.

The initial dosage employed is probably too low to be effective. Significant changes in blood phospholipid were not seen in our series in less than 12 weeks on six capsules a day, although by 10 months the treated group shows a marked rise. Effective treatment in their series was probably therefore only about one month. In particular, our findings for the two substances they have indicated differ from theirs. The cholesterol levels in our series actually rise after the drug is administered. Mean levels are plus 44 mg. at 6 weeks, plus 39 mg. at 12 weeks, with return to nearly normal levels at 30 weeks. The control group, of equal size and randomly selected, does, however, show a similar change. Pre-beta lipid, when assessed by the method of Dr. E. B. Smith, to which they refer, and in which account should also be taken of the position of the boundary, behaved in identical fashion in both groups. However, when assessed electrophoretically as a fraction of total beta-lipoprotein, which has itself been assessed by flocculation with heparin, differential progressive changes

are seen. While the untreated group remains unchanged over 12 weeks, those treated show approximately a 30% improvement.

In my view too much attention is paid to cholesterol. If plaques are to be mobilized levels will probably rise in a patient who is improving. All workers agree that pre-beta lipid is very difficult to assess quantitatively and a positive result is of more value than a negative one. Furthermore, I do not think that three months is long enough nor ten cases a large enough series to justify any comments on "the natural history of the disease." There are now over 90 papers on this drug in the world literature, but this is the first I have encountered in a British journal. The overseas reports are mostly favourable although not wholly convincing. I think it would be wise to suspend judgment on the value or otherwise of this preparation until we have some clinical data on its use under our own epidemiological conditions.—I am, etc.,

East Ham Memorial Hospital, London, E.7. J. B. Enticknap.

Oral Treatment of Pernicious Anaemia

Sir,—The recent article by Dr. E. K. Blackburn and his colleagues (*Journal*, September 26, p. 535), and your leading article (p. 554), prompt me to make available to the readers the results of our own investigations on the same subject.

In 24 pernicious-anaemia patients treated with "biopar" and later with "biopar forte" for periods of 3½ to 4½ years, the concentration of vitamin B_{12} in the serum was determined using the microbiological assay with *Euglena gracilis* var. *bacillaris*. Prior to biopar 20 of 24 patients underwent treatment with 4-ml. single doses of "anahaemin" (B_{12} content: 2.5 μg./ml.) at 3- to 8-weekly intervals, three were treated with injections of crystalline vitamin B_{12} ("cytamen"), and one received biopar from the start. It was found that after biopar treatment only three patients had a normal vitamin level (>150 $\mu\mu$g./ml.) and in 15 it was very low (<80 $\mu\mu$g./ml.). Signs of a haematological relapse (partly megaloblastic erythropoiesis) were common in the group with serum levels of <60 $\mu\mu$g./ml., but occurred also at levels higher than this (<100 $\mu\mu$g./ml.). Contrary to the results of Dr. Blackburn and his colleagues, no relapse has been observed in cases with normal levels: had this been so it would have suggested an interference with the utilization of vitamin B_{12} by the bone-marrow, a state of affairs hitherto unknown. Megaloblastic erythropoiesis with normal vitamin-B_{12} levels is in most cases indicative—as far as is known—of a folic-acid deficiency or of interference with folic-acid metabolism—e.g., by anticonvulsants.

In 16 patients treated with biopar we were able to study the effect of two intrinsic-factor preparations (I.F.)—supplied by Drs. Williams and Ellenbogen, of the Lederle Laboratories, and by Mr. D. Purdie, of the Armour Laboratories—on the absorption of orally administered radioactive vitamin B_{12} (containing cobalt-58). The only three cases in which I.F. improved absorption were those in whom a normal B_{12} serum level had been found by the *Euglena* assay method.

The position is not much happier with the vitamin-B_{12}–peptide complex of Heathcote and Mooney, referred to in your leading article. This preparation was administered in doses recommended by the makers, i.e., one to three 100-μg. B_{12}-containing tablets daily for the initial treatment, and gradually reduced to one 20-μg.-containing tablet per day. While all patients had a fairly satisfactory haematological response, this was not better than what would have been expected after the oral administration of the same amount of pure vitamin B_{12}.[1] In 2 out of 10 patients thus treated the serum level did not rise to normal in spite of a haematological improvement, and it was necessary to administer vitamin-B_{12} injections. In two cases transferred to a 20-μg. daily maintenance dose, the serum level of the vitamin dropped to pre-treatment levels in a few weeks' time. In one patient after an initial rise there was a decline of the serum-B_{12} level in spite of a high maintenance dose (one 100-μg. tablet daily). It is difficult to say whether this was due to the development of a refractoriness similar to that appearing after biopar, or to variations of the "distivit" vitamin-B_{12} content.

It is almost certain that the continuation of oral therapy using a vitamin-B_{12} + intrinsic-factor preparation, such as biopar, would lead ultimately to a relapse of the disease in nearly all cases thus treated. This is due to the development of refractoriness to the absorption of such preparations in 87% of cases according to our observations.

Oral treatment of patients with both vitamin B_{12} + intrinsic factor (biopar and similar) or with "peptide-complex" preparations (distivit) is not to be recommended. And I would add as a further reminder that liver injections if used at all in treatment of true pernicious-anaemia cases should be assayed for their content of vitamin B_{12}, and the dose adjusted accordingly. Parenteral vitamin B_{12} is hitherto still the most economical and most reliable means of treating pernicious anaemia patients.—I am, etc.,

City General Hospital, Sheffield, 5. S. Varadi.

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1 Chalmers, J. N. M., and Shinton, N. K., *Lancet*, 1958, **2**, 1298.

Serum Amylase

Sir,—In discussing the value of serum amylase estimations in the differential diagnosis of acute abdominal emergencies (*Journal*, October 3, p. 602), Dr. Roger Chapman fails to emphasize the importance of the frequent rise of serum amylase in renal disease. Heifetz *et al.*[1] first showed that impaired renal function is usually associated with a retention of amylase in the blood and a diminished excretion in the urine. Acute renal failure may present as an acute abdominal emergency. This is illustrated by the history of a woman, aged 43 years, who was admitted to the Middlesex Hospital with an indefinite history of duodenal ulcer of 10 years' duration.

For two weeks she had been vomiting, and now complained of severe epigastric pain going through to the back and to both shoulders. On examination she looked ill and was in pain. She was pale, her breathing was laboured, and she had foul-smelling breath. Blood pressure was 150/85. A pericardial rub was heard.

Because of the distribution of the pain, it was thought possible that she might have acute pancreatitis, while her other signs suggested uraemia. She was found to have a blood urea of 510 mg./100 ml. and a serum amylase of 1,600 units. The latter was repeated the following day and found to be the same, while the blood urea had risen to 600 mg./100 ml. Her condition deteriorated in spite of treatment and she died two weeks later. At necropsy her pancreas was completely normal, both macroscopically and histologically, while her kidneys showed the changes of chronic pyelonephritis.

In a further two patients, I have found serum amylase values of 4,000 units and 800 units associated with blood urea values of 260 mg. and 350 mg./100 ml., respectively, in whom there was no clinical evidence of pancreatic or bile-duct disease. These cases demonstrate that it is misleading to rely on a raised serum amylase

value without estimating the blood urea even when acute pancreatitis or some other abdominal emergency is suggested clinically.—I am, etc.,

PAUL TURNER.

The Middlesex Hospital, London, W.1.

REFERENCE

1 Heifetz, C. J., Probstein, J. G., and Gray, S. H., *Arch. intern. Med.*, 1941, **67**, 819.

Bemegride and Pregnancy

SIR,—Contradictory opinions have been expressed in the Continental literature as to whether or not bemegride ("megimide") may be used during pregnancy, for fear of an adverse effect on the uterus or foetus. Graham and Nicholls[1] have shown that ^{14}C-labelled bemegride passes rapidly from rat maternal blood to the foetus, and moves slowly into the amniotic fluid. It may be expected from studies on maternal tissues to persist at a low level for 24 hours and longer. Work done in this laboratory by Mr. Nicholls has shown that bemegride has no direct effect on muscular activity in the uterus of rats, rabbits, and guinea-pigs, except in high concentrations which could not be attained during therapy because of the convulsant action. This effect is a depressant one.

Recently, an unmarried woman aged 46 years, six months advanced in pregnancy, was admitted to St. David's Hospital, Cardiff. She had taken approximately 24 gr. (1.6 g.) of quinalbarbitone some 12 hours before in a fit of depression, and was in coma. The blood level was 3 mg./100 ml. She was anaesthetic, the light and pharyngeal reflexes were very sluggish, and others absent apart from flexor plantar responses. Respiration at 18/minute was deep and aeration good. Pulse rate was 116/minute, pressure 120/80 mm. Hg, and she was dehydrated. She was given an infusion of 2 litres of glucose saline and injections of 125 mg. of the sodium salt of bemegride, made every 20 minutes, to a total of 3.5 g. before she was considered to be safe. Unconsciousness lasted 12 hours or more before admission and 18 hours thereafter, with complete recovery and no evidence of toxicity.

At no time was there any distress of the foetal heart or uterine disturbance, and pregnancy has continued uneventfully.

Pregnancy is not a contraindication to therapy with bemegride.—I am, etc.,

J. D. P. GRAHAM.

Department of Materia Medica and Pharmacology, Welsh National School of Medicine, Cardiff.

REFERENCE

1 Graham, J. D. P., and Nicholls, P. J., *Brit. J. Pharmacol.*, 1959, **14**, 35.

Peptic Ulcer in Africans

SIR,—The burden of your annotation (*Journal*, June 6, p. 1462) on this subject is that peptic ulcer, shown by Raper[1] to be of much the same frequency among Uganda Africans as among people in England and Scotland, is yet relatively seldom recognized clinically. While we agree that the latter is often true, and this not surprisingly in areas far from the larger medical centres, it is unfortunate that several of the statements you quote are somewhat dated. It would be unfortunate, too, if the great weight of Sir Stanley Davidson's experience gleaned on a rapid tour of Africa[2] should help to perpetuate a belief in the rarity of peptic ulcer in Africans. That peptic ulcer is recognized as a routine clinical problem in equatorial Africa is clear from the more recent reports from Uganda and the Belgian Congo which you quote and from observations of Konstam[3] and Rose[4] in West Africa. Their observations are mostly on patients submitted to surgery, and it is pertinent to comment at this point on the content of the operations register as found in many African hospitals. How many hundreds of the 7,000-odd operations in the pre-war Uganda hospital were for hernia, urethral stricture, trachoma, tropical ulcer, and traumatic surgery of a kind which would rarely figure in a British surgeon's operating-list? How easy is it to find a surgical bed, even in post-war East Africa, for a "cold" surgical case? Thus the incidence of peptic ulcer surgery, though still small by European experience, is not quite so disproportionate as it appears at first sight.

It may be of interest to record our experience[5] on the medical wards at Mulago Hospital where Raper's observations were made. During 1957 some 70 patients admitted to the medical wards were considered to have peptic ulceration. While this may seem a very small proportion of the 2,500 medical admissions for that year it must be remembered that some 35% of our patients are admitted for acute infections such as pneumonia, typhoid, meningitis, and malaria, which correspondingly weight the statistics. As many patients again are seen and treated for peptic ulcer in the out-patient clinic and did not require admission to the wards. Cirrhosis of the liver is accepted as having a very high incidence in tropical Africa, and yet in 1957 we admitted as many patients with peptic ulcer as with cirrhosis of the liver. Of the 70 in-patients 50 were male and 20 female, a sex incidence in keeping with the male:female admission ratio of 2.5:1. Fourteen patients had their condition radiologically confirmed, 7 of these having pyloric obstruction, and a further 14 were confirmed at operation. The remainder were diagnosed as having a peptic ulcer on their history and response to treatment, and one might add that the history is often as clear and typical as any encountered in English hospitals. Characteristic nocturnal pain is frequently present and haematemesis was a presenting feature in 10% of those admitted to the medical wards. Gastric ulcer is very rarely found either at operation or on barium-meal examination, and thus our clinical findings are much in keeping with Raper's observations on necropsy material.

A further 14 patients were admitted directly to the surgical wards, 5 with pyloric stenosis, 6 with acute perforations, 2 with active duodenal ulcers, and 1 patient with a prepyloric gastric ulcer. The youngest patient seen in the whole series was an 11-year-old boy with a two-year history of symptoms and an extremely large duodenal ulcer with pyloric obstruction, confirmed at operation. As most patients find it extremely difficult to cope with the regime of medical treatment at home in the villages, the response to treatment observed in the wards is seldom of long duration and operation is frequently considered necessary.

Although a few of the patients in this series were well-educated or relatively well-to-do, the majority were small farmers, herdsmen, or casual labourers, and this aspect of the condition has previously been noted in discussions on peptic ulcer in Uganda. In the Student Health Service at Makerere College, peptic ulcer is a fairly common clinical diagnosis, and over one period of two years some 19 cases were seen, 5 radiologically confirmed[6] in a population at risk of 400 undergraduates drawn from all over East Africa. Amongst the nursing staff at Mulago Hospital, again the condition is not infrequent, and, of 30 nurses admitted to the Sick Bay in 1957 for conditions other than upper respiratory infections, influenza, and malaria, 7 were found to have peptic ulcer, 4 confirmed radiologically.

It causes us no surprise that only 5 of Raper's necropsy series were known to have been diagnosed clinically. Most patients in whom we recognize peptic ulcer evade immediate transfer to the post-mortem

room, and it must not be assumed that none of those observed as necropsy scars had been diagnosed while active, since the clinical records available to the pathologist related in most cases to the patient's last illness only. One explanation of why many peptic ulcers in that series may have passed unrecognized is inherent in Raper's own criteria. What do the scars he records represent? We may be sure that many had at some time been sufficiently large, active, or persistent to produce symptoms, but we do not know what proportion had been silent or transient.

We agree with you, Sir, and with Raper that peptic ulcer is far more important in African practice than is yet generally recognized. Much of what Raper says of peptic ulcer could be said of other "non-tropical" disorders. The hospital population in Africa, and the rapid turnover of minor ailments and infections, are such that even where a condition like peptic ulcer is familiar and well recognized its place in the admissions or operations register will often not reflect its clinical importance. Not until preventive and domiciliary medical practice develop sufficiently to draw off much of the illness and injury which nowadays fill African hospitals, and not until the outlook of practitioners in the tropics reflects more nearly that of the general physician than the tropical parasitologist, will peptic ulcer, hypertension, diabetes, and many other medical problems in this continent be seen for what they are.—We are, etc.,

A. G. Shaper.
A. W. Williams.

Department of Medicine,
Makerere College,
Kampala, Uganda.

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2 Davidson, L. S. P., *Lancet*, 1954, **1**, 614.
3 Konstam, P. G., ibid., 1954, **2**, 1039.
4 Rose, J. R., ibid., 1955, **1**, 107.
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6 Allbrook, D. B., ibid., 1958, **35**, 97.

Qualification in Medicine

Sir,—When I first qualified in medicine some 30-odd years ago—and, in fact, for many years afterwards—I used to think that degrees were everything. I now know that they can mean very little, and that the ability to write a thesis is no criterion of one's ability as a clinician. At the risk of being thought highly prejudiced, some of the best clinicians and the most enthusiastic doctors have, in my experience, been London Conjoint men. On the other hand, I have known men with higher qualifications who for one reason and another have been in general practice to treat their patients as if they and their ailments were quite unworthy of their superior attainments.

Let us, however, who were trained below the Border not forget that the doctor-hero of any book or play has almost invariably got a Scotch name and has usually been trained at Edinburgh. Be that as it may. "The rank is but the guinea's stamp; The man's the gowd for a' that!" And that is certainly very true in medicine.—I am, etc.,

Bath, Somerset. G. L. Davies.

Sir,—In reply to the comments of Drs. I. M. Larkin and Marjorie M. Dobson (*Journal*, September 26, p. 581) on my letter under the above heading, I would like to say that it is a delusion, at times held by all of us, that passing examinations, either "higher" or "lower," confers any real or permanent distinction in medicine. In practice we judge our colleagues not by the letters after their names (unintelligible to laymen and regarded with some cynicism by the profession), but by their standard of actual work based on knowledge required in the hard school of long experience.

European universities as venerable as that of Cracow have not regarded it as "debasing" to grant an M.D. as a first medical qualification. The M.D.(Lond.) and that of our other universities has always been far easier to obtain than the corresponding D.Sc., and since the nationalization of medicine in this country it has certainly suffered some devaluation, at least in so far as obtaining appointments is concerned.

To refer to any of our Royal Colleges as "revered" can only raise a wan smile since the events of 1948. The M.R.C.P. and F.R.C.S. used to be taken by a small number of candidates after long experience and mature reflection; now one sees an undignified scramble for these diplomas for motives mainly concerned with securing a lucrative appointment under the Health Scheme.

I stated in my letter what is wrong with the London M.B. I am indeed ashamed to obtain a degree by a series of glib answers to questions on "the small print stuff" of medicine in place of a searching examination in the fundamentals of the subject; the latter procedure would raise, not lower, the standard. Your correspondents seem to think it rather a good thing to make examinations "difficult"; personally I think it is merely a sign that we do not trust the quality of our students or the adequacy of their training, and thereby lies the road to improvement—with fairer examinations at the end of it.—I am, etc.,

Welwyn Garden City, Herts. G. O. Morse.

Sir,—Regarding the medical qualifying degrees discussed by Dr. G. O. Morse (*Journal*, August 15, p. 190), Dr. J. R. Rees (September 5, p. 366), and Drs. M. M. Dobson and J. R. Rees (September 26, p. 581), may I quote remarks made to me as an intern in two hospitals in the U.S.A. in 1956 and 1957 when I used the M.B., B.S. designations, and attempted to explain other titles, diplomas, and abbreviations, which the Americans could not grasp?

Medical Student: "How can you be called 'Doctor' if you don't even have an M.D. degree?"

Professor of Surgery: "What do you want to do the F.R.C.S. for? It's only an examination in anatomy. Don't even have to have performed a single operation!"

Patient: "If you're only a Bachelor of Medicine that ain't as high as a Doctor of Medicine. You must be only a stoodunt."

Resident: "You spoke of Mr. Somebody and surgeon in the same breath. We don't let anybody but qualified doctors perform any surgery here."

Another Intern: "Why do you bother to list the B.S. for your Bachelor of Science degree at all?"

All communications were addressed to us as M.D. The diplomas conferred at the end of the internships were inscribed M.D. I sent my first one back for correction to M.B., B.S., and the superintendent was exasperated. When the second diploma came inscribed M.D. I didn't bother—"Man is always explaining and is never understood."

I am all for uniformity of degrees conferred, of course, but let us find out if the original qualification in medicine was Doctor, and if it was subsequently and

insidiously replaced by Bachelor, while our predecessors still cling to the traditional right of being addressed as Doctor. Which one will you have: M.D.(Lond.), M.D. (R.C.S. and R.C.P.), M.D. (S.A.) ?—I am, etc.,

W. G. FOGLAND.

Birmingham and Midland Eye Hospital,
Birmingham, 3.

Acrylics in Neurosurgery

SIR,—I am very glad that Mr. John Dutton (*Journal*, October 3, p. 597) has been able to confirm our work on the ease of bacterial contamination of cold-curing acrylic resins.[1] We have had considerable difficulty in persuading many of our neurosurgical colleagues and the manufacturers of this type of product that it cannot be used without due regard to sterility. Our solution of autoclaving the polymer destroys the accelerator. It thus appears that a mixture of the polymer and monomer merely sticks the grains of the polymer together, and excess monomer is lost by absorption or evaporation. Nevertheless, I have found this end product acceptable for cranioplasty in spite of a small degree of shrinkage of the finished plate.

The way now would seem clear for the manufacturers of the cold-curing acrylic resins to put up properly sterilized components and not allege this is a self-sterilizing mixture.—I am, etc.,

RICHARD G. ROBINSON.

Department of Neuropathology,
Institute of Psychiatry,
Maudsley Hospital,
London, S.E.5.

REFERENCE

[1] Robinson, R. G., and Macalister, A. D., *Brit. J. Surg.*, 1954, **42**, 312.

When to Tie the Cord

SIR,—It is quite a long time since I had to deal with an umbilical cord (*Journal*, September 12, p. 432), nor have I even seen one since I retired several years ago, so perhaps I may be considered somewhat out of date. I used to tie the cord as soon as the baby was born for the following reasons, which seem to me to be logical and sound.

The general teaching is, quite rightly, that the baby should retain as much of its blood as possible without engorgement. That implies that (*a*) as little blood as possible should be pumped out, and (*b*) as much should be returned as possible before the cord is tied. There is only one source of power by which the blood pumped out can be returned to the baby and that is the baby's own heart contractions. The intermittent and unreliable uterine contractions are of little or no account in this matter. Also delay in dealing with the cord may allow of some detachment of the placenta and so lead to direct loss of blood. The baby's heart pumps blood into the placenta, still *in utero*, the placenta itself becoming like an inert lake of blood resisting the inflow and getting more and more engorged. Does it seem reasonable to expect this small heart to be able to force more than a modicum of blood through this inert and heavy lake and cause it to be returned to the baby without loss ? I am sure that the longer the delay in tying the cord the more blood will be pent up in the placenta and the less will be restored to the baby. Therefore the cord should be tied right away after the baby is born.—I am, etc.,

Edinburgh. A. E. CHISHOLM.

Treatment of Migraine

SIR,—Your annotation on the treatment of migraine (*Journal*, July 18, p. 69) appears to be a determined attempt to return to the days when we had little understanding of its mechanism or background. Once the diagnosis of migraine—distinguished from other headaches with vomiting or nausea—is established, almost all cases are "idiopathic" unless they belong to the group occurring later in life with cerebral vascular sclerosis. It must be extraordinarily rare for migraine to be the presenting symptom of internal carotid thrombosis or other "organic" diseases. Whilst it is true that there are cases of true migraine precipitated by visual factors, the great majority of headaches with nausea relieved by spectacles are not migraine but are symptoms of severe ocular fatigue.

Migraine is surely the supreme example of a malady in which the degree of suffering depends upon the sufferer—and upon the advice he is given. Its manifestations are aggravated by relaxation, and to treat a mild attack by rest in bed may well make it a severe one. Our sympathies and efforts should aim not at persuading the patient to lie down under his affliction but at urging him to rise above it. To see that he "regulates his life to a steady pattern, free from anxieties and stress" is to submit the patient to his malady and to fail in our duty to enable him to face life normally.—I am, etc.,

Redruth. CHRISTOPHER HEATH.

Syphilis and Mental Deficiency

SIR,—The article "Syphilis as a Cause of Mental Deficiency," by Drs. J. M. Berg and Brian H. Kirman (*Journal*, September 12, p. 400), is interesting, and reminds present-day doctors of facts which should be well known, with modern and up-to-date information. I most certainly would not agree that the cases of syphilis (or V.D. generally) as treated at centres—and therefore the basis of official statistics—are a sure indication of the real occurrence. This has been stated before but will bear repeating until officially noted.

It may be that the disease is decreasing—and probably is so. There are, however, a large number of cases treated in general hospitals in medical and neurological units, and in antenatal clinics, that never reach the centres, so that the official statistics are at best a guide. This may be true principally in London and major cities, but nevertheless occurs elsewhere. I personally have seen frank G.P.I. and tabes, as well as the more numerous early cases (other than primary sores), picked up from routine admissions to a medical ward on numerous occasions.—I am, etc.,

London, W.1. J. D. REDMILL.

The Fossil Skull of Olduvai

SIR,—The issue of the *Journal* for September 19 (p. 487) carried an annotation giving information concerning the new and important fossil cranium discovered by Dr. and Mrs. L. S. B. Leakey on July 17 in the Olduvai gorge, Tanganyika. The author of that annotation gave some account of the anatomical peculiarities of the Olduvai specimen, stressed the australopithecine character of the palate and dentition, and stated that "the mastoid processes and zygomatic

region are of hominid configuration." He alluded to Dr. Leakey's claim that *Zinjanthropus* was annectent between the Australopithecinae and the undoubted hominids, but, on the basis of published photographs of the Olduvai discovery, regarded this new primate fossil as essentially an australopithecine, not far removed, perhaps, from *Paranthropus*. Thereafter he proceeded to deplore the arbitrary multiplication of generic and specific names as particularly unhelpful in the study of the human palaeontological record, and expressed the hope that for Dr. Leakey's erection of the new genus *Zinjanthropus* there was "good anatomical reason" as yet undisclosed.

To this annotation Dr. Leakey took vigorous exception in the issue of the *Journal* for October 3 (p. 635). He claimed that, at the time of composition of the offending annotation, the sole photographs of the new fossil released for publication were of the palate only (*The Times*, September 5; *Illustrated London News*, September 12). He resented the implication that *Zinjanthropus* was an arbitrary generic creation and promised an early publication in *Nature* justifying his taxonomic gesture. Meantime he invited the unknown author of the annotation to attend his British Academy lecture on the Olduvai find on October 7 "to learn a few facts about the skull before he comments further."

Some anatomists who did attend that lecture were disappointed. Whilst in configuration the mastoid region, zygomatic arch, and temporal fossa of *Zinjanthropus* proved the contrary of "hominid," little if any anatomical evidence was advanced concerning the cranium additional to the information already provided by the excellent photographs appearing in the *Illustrated London News* for September 19. No "good anatomical reasons" were submitted for the granting of generic rank to the Olduvai specimen. The sum total of the anatomical evidence—particularly the details of nasal fossa, facial skeleton, sagittal crest, temporal flanges, and nasal bones—proclaimed the fossil's undoubted australopithecine organization, which its discoverer freely accepted.

Dr. Leakey, however, seemed to fall into the very error of which he had accused the writer of the *Journal* annotation—i.e., of making statements unwarranted by available evidence. For it transpired that the illustrations of the Olduvai cranium used in the lecture (essentially those familiar from the *Illustrated London News*) were no longer valid representations of *Zinjanthropus* cranial morphology. Repair and restoration of the Olduvai cranium were still in progress and photographs so far published represented, not the final form of the reassembled cranium, but merely stages, since considerably modified, in the business of reconstruction. It was stated, for example, that the facial skeleton had required readjustment so as to render the cranium much more orthognathic than at first supposed, and that further readjustment might prove necessary.

Nobody can quarrel with readjustments of this sort, dictated by the requirements of morphological accuracy, and even a partial or inaccurate reconstruction of such a fossil does suffice to make manifest some at least of its more obtrusive anatomical features. But it is much to be regretted that a complete and anatomically accurate reconstruction was not effected before the publication of photographic representations of the *Zinjanthropus* cranium. With every sympathy for Dr. Leakey's enthusiasm in seeking early and public recognition of his remarkable find, it remains the fact that no satisfactory appreciation, or discussion, of *Zinjanthropus* distinctive morphology is possible in the absence of a complete and anatomically accurate restoration. Statements of scientific validity cannot be made upon an unfinished restoration nor can dependable inferences be drawn therefrom touching a variety of relevant physiological considerations.

Until such final restoration is effected (and, it is hoped, reliable casts made available) criticism and comment are necessarily inhibited: the exact morphological constitution of the Olduvai specimen remains unknown and its discoverer's assessment of its taxonomic status incapable of satisfactory evaluation. It is therefore most earnestly to be hoped that the very numerous fragments of the *Zinjanthropus* cranium will be totally assembled with all the speed compatible with the meticulous accuracy inseparable from such a task, and that, this done, casts of the final restoration will be made generally available with all promptitude.

Dr. Leakey's archaeological zeal and acumen have notably enriched the palaeontological record by a discovery of singular importance: he will increase the indebtedness of anatomists and anthropologists if he now ensures the necessary sequel of craniological reconstruction with comparable skill and dispatch.—I am, etc.,

Department of Anatomy, St. Bartholomew's Hospital Medical College, London, E.C.1. A. J. E. Cave.

Steely Eyes and Pain

Sir,—Change in the colour of the eyes can accompany not only pain (*Journal*, September 12, p. 418) but other causes of lack of "ease," such as anxiety states. For instance, a woman remarkable for the blueness of her eyes, suffering from a third recurrence of pulmonary tuberculosis, was operated upon successfully some seven years ago, since when she has returned to hospital at intervals for check-up. These check-ups are arranged by herself at the convenience of her consultant. Thus, though the periodicity of check-up is known to her large household, the actual week and date of forthcoming examination are not known. None the less it is common knowledge within the household that a check-up is imminent, for "X's eyes have gone grey." Only to her most intimate friend, and then only with the greatest reluctance, will she admit to the depth of anxiety suffered in anticipation of the forthcoming examination—after which the eyes immediately regain their blueness and brightness.

This phenomenon is an example of what in Peckham we recognized as action-pattern: in this case of (returning) health, or "ease"—from which anxiety has retreated.—I am, etc.,

Rotherfield, Sussex. Innes H. Pearse.

Papular Urticaria and Parasites

Sir,—I recall reading, quite some time ago, a letter discussing the possible parasitic origin of papular urticaria and the relatively successful treatment of the condition with parasiticides (*Journal*, June 9, 1956, p. 1365). At the time this interested me profoundly, as I had noticed two salient features of the condition in general practice—viz., (1) the occurrence in "epidemics" mainly in spring and autumn, and (2) more than one member of a family being affected at the same time. This seemed to suggest an infective origin.

Last spring I collected a series of 60 cases and treated them alternately, using (*a*) the orthodox treatment of diet, oral antihistamine, and a local antipruritic lotion, (*b*) emulsio benzyl benzoate used as for scabies. Where more than one member of a family was affected, I treated the children by alternate methods. I found no significant difference using the parasiticide, and, in fact, in a number of cases those treated by the more conventional method appeared to do better.

As I still feel strongly that there is an infective factor in the aetiology, I wonder if any of your readers have had similar or completely different results, or have any further comments to make on this very common but distressing condition.—I am, etc.,

Glasgow, S.3. GERALD M. JESNER.

Purpura in Kwashiorkor

SIR,—We should like to state in reply to Dr. Z. A. Leitner's letter (*Journal*, August 29, p. 303) that the purpuric lesions referred to in our paper were proved histologically to be due to haemorrhages.—We are, etc.,

E. KAHN.
H. STEIN.

Johannesburg, South Africa.

Motor-cycle Accidents

SIR,—Dr. Myer Goldman (*Journal*, September 19, p. 501) quotes and endorses Mr. Kenneth Wood's remark that "a boy of 16 . . . can ride a most powerful machine—something capable of more than 130 miles per hour—on the first day on which he chooses to sample the perilous roads of to-day." No standard motor-cycle sold in this country will attain 130 m.p.h. (230 k.p.h.) or anything like it. Let us not in any case blame the boy of 16 for taking a fast motor-cycle on the roads without previous experience when the system allows him to do so.

There is a simple and effective solution to this problem of gaining experience with a motor vehicle on the roads. This solution is widely practised on the Continent, but not, alas, in Britain. The means is the moped, which is, in effect, a motorized bicycle equipped with pedals and an engine of not more than 50 c.c. This little machine is capable of about 30 m.p.h. (48 k.p.h.). The suggestion, which has already been put before the Government, is that boys and girls of 15 should be permitted to ride mopeds, as they are on the Continent, but no other motor vehicle. When they reach the age of 16 they will then have had a year's experience of a light, low-powered machine before moving on to something bigger. Mopeds have the best road-safety record of any motor vehicle. Their use should be encouraged.

As a further positive aid to the cause of road safety through the training of young motor-cyclists, I suggest that in addition encouragement be given at an early date to the teaching of motor-cycling in schools, and that urgent official help be given to the excellent R.A.C./A.C.U. training scheme for motor-cycle and scooter riders.—I am, etc.,

HILARY WATTS.
Public Relations Officer, British Cycle and Motor-cycle Industries Association Ltd.

London, W.C.2.

Tongue-tie

SIR,—May I beg space in your columns to endorse the opinion of Dr. S. C. Rogers (*Journal*, October 3, p. 633)? During my 23 years in charge of the Speech Therapy Department of Guy's Hospital cases were referred to me from time to time for my opinion whether or not an operation was necessary. In every case I found that the tongue had ample freedom for all its positions required for fluent speech.—I am, etc.,

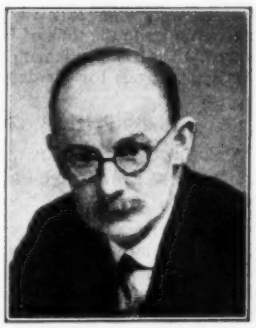
London, N.W.1. H. ST. JOHN RUMSEY.

Obituary

R. RUTSON JAMES, F.R.C.S.

Mr. R. Rutson James, consulting ophthalmic surgeon to St. George's Hospital, died peacefully at his home at Woodbridge, Suffolk, on September 28, one week before his 78th birthday.

Robert Rutson James was born on October 6, 1881, the eleventh child of the Rev. Alfred James, rector of Burwarton, Salop. His grandfather, William James, was Radical M.P. for Carlisle for nearly 30 years, and had served as high sheriff for Cumberland. From Winchester College Robert James entered St. George's Hospital Medical School in 1899, and qualified towards the end of 1905. He took the F.R.C.S. in the following May, but had to wait until his 25th birthday to be admitted a Fellow. After qualification he held resident posts at St. George's Hospital, at Moorfields, where he worked under William Lang and Sir John Parsons, by whom his career was much influenced, and at the Royal Westminster Ophthalmic Hospital under E. W. Brewerton and W. H. McMullen. He returned to St. George's as ophthalmic registrar in 1909 and was elected assistant ophthalmic surgeon a few months later, a post he held for 17 years, and he was ophthalmic surgeon to the West Ham (now Queen Mary's) Hospital from 1911 to 1918. Dean of the medical school at St. George's from 1918 to 1922, he was treasurer of the school from 1925 to 1927. He was ophthalmic surgeon to the hospital from 1926 to 1931, when he was appointed to the consulting staff. He retired from his private practice in 1939 and went to live at Woodbridge. Rutson James was honorary secretary of the Ophthalmological Society of the United Kingdom from 1918 to 1921, and later served on its council. He was Bowman librarian from 1924 to 1927, and received the unusual distinction of honorary membership of the society in 1936. He edited the society's *Transactions* from 1939 to 1945, and was sub-editor of the *British Journal of Ophthalmology* from 1924 to 1929 and then editor for 20 years.



By temperament a scholar and an antiquary, Rutson James transcribed and annotated the registers of admissions at St. George's Hospital Medical School from 1759 to 1918 and the registers of the Barber Surgeons Company from 1540 to 1745. These and similar products of his untiring industry and accurate scholarship he deposited in the library of the Royal College of Surgeons of England, to which he was a generous benefactor, so that they might be available to historians. He also presented his outstanding collection of the bookplates of medical men. He made many contributions to his own and other journals on clinical and historical subjects, and published three historical books: *The School of Anatomy adjoining St. George's Hospital, 1830–1863* (1928), *Studies in the History of Ophthalmology in England prior to 1800* (1933), and *Medical Practitioners in the Diocese of London, 1529–1735* (1935). He married in 1910 Miss Margaret Newson, who died last March. He is survived by their only daughter.

H. B. S. writes: R. Rutson James was born and bred in a West-country parsonage. His childhood experiences in observing parental management of village folk and their problems contributed much to his humanity, his constant and sensitive consideration for the feelings of others, his abounding patience and kindness. Educated at Winchester

College, he was an admirable example of "Manners makyth man." His courtesy, always so genuine, was constant whoever he addressed; in hospital practice, the rough navvy, or the bewildered old lady, or the apprehensive child. As an eye surgeon, he was scrupulous and conscientious, and in his clinical work his powers of observation were acute, shrewd, and accurate at a time when the instrumental aids to the minute examination of the eye were simple and less elaborate than is the case to-day. Shy, hypersensitive, and retiring, he preferred to have a small private practice of devoted patients. It was probably the inevitable stresses of surgical work which caused him to retire prematurely from his hospital appointments and practice to seek a happy retreat among his books. He was an erudite scholar who maintained throughout his life a love of classical literature, history, and archaeology. His writings were in impeccable English and his annotations charged with whimsical wit. As a proof-reader he had no peer, even up to the time of his death. He was an admirable doctor, a perfect gentleman, a generous and lovable friend. Our sympathy is for his daughter, who survives him.

PHILIP GOSSE, M.D.

Dr. Philip Gosse, doctor, naturalist, and author, died at his home at Cambridge on October 3. He was 80 years of age.

Philip Henry George Gosse was born on August 13, 1879, the only son of Sir Edmund Gosse. Leaving Haileybury College to enter an agricultural college in Lincolnshire, he then accompanied the FitzGerald expedition to the Andes as naturalist in 1896–7. Soon after his return he was sent to Cambridge by his father, and read medicine at Trinity College, going on to St. Bartholomew's Hospital to receive his clinical training. He qualified M.R.C.S., L.R.C.P. in 1907, and in 1923 was granted the M.D. of Durham. After qualification he held the appointment of house-surgeon at the Essex County Hospital, Colchester, and then entered general practice in a village in the New Forest. During the first world war he served with the R.A.M.C. in France and India. After the war he was a medical referee to the Ministry of Pensions, and, later, medical superintendent of the Radium Institute, London, from which post he retired in 1930.

Gosse was a man of multifarious interests. He is credited with saying that he had "failed in life" because he had too many interests and that he cultivated a new hobby every few years. Nevertheless, he made his mark as a naturalist, and as a historian he published several volumes. In 1939 his collection of books on pirates and piracy was presented by an anonymous donor to the National Maritime Museum, Greenwich. So far back as 1899 Gosse published his *Notes on the Natural History of the Aconcagua Valleys*, and subsequent work from his pen included *Birds of the Balearic Islands* and *Mammals of Flanders*, and a biography of Charles Waterton, the naturalist, entitled *The Squire of Walton Hall*. He produced *The Pirates' Who's Who* in 1924, *My Pirate Library* in 1926, and *The History of Piracy* in 1932. A widower, he was three times married. He had a daughter by each of the first two marriages.

A. J. D. S. writes: A catalogue of Philip Gosse's medical career ignores, to say the least, much that was important, and he himself confessed that medicine had not been of his own choosing. It was perhaps natural—his father was Sir Edmund Gosse and his grandfather Philip Henry Gosse, the naturalist—that his interests should lie in the study of birds and animals and in writing. Apart from his works on natural history and his entertaining autobiographical studies, he covered a wide field. Perhaps the most important of his books were the *Life of Sir John Hawkins*, *St. Helena*, and the fascinating *History of Piracy*. He had a host of friends, not only in this country, but all over the world, and his large correspondence, which he conducted with great wit and enthusiasm, gave him enormous pleasure. One of the many things for which he will be remembered with affection was his interest in the Fountain Club, a dining club of old Bart's men. He was one of its founders and was responsible for its conduct over many years. He still went to the club dinners, though not as often as he would have liked, and was looking forward to the celebration of its fiftieth anniversary. Philip remained young in heart and mind and was active to the end, and the end came for him after a sudden illness which overwhelmed him in a few days. Those who knew him rejoice that his kindliness, wit, and friendliness were not dimmed by gradual failure, but remained vivid and memorable to the end.

E. L. CALDWELL-SMITH, O.B.E., M.B., B.Chir.

Dr. E. L. Caldwell-Smith, formerly chief medical officer to the Shipping Federation and Merchant Navy Establishment, died at his home at Wimbledon on July 16. He was 67 years of age.

Eric Lauder Caldwell-Smith was born on January 3, 1892, the son of Dr. P. C. Smith, for many years medical officer of health for Wandsworth. From Oundle School he entered Trinity College, Cambridge, where he took his B.A. in the Natural Sciences Tripos in 1913. Going on to St. Thomas's Hospital for his clinical training, he qualified M.R.C.S., L.R.C.P. in 1915, and four years later he took the degrees of M.B., B.Chir. His medical studies were interrupted by the first world war, when he served as a temporary surgeon in the Royal Navy. For some time he worked as an anaesthetist at naval hospitals, and after his return to civilian life he held appointments as honorary anaesthetist to the Metropolitan Ear, Nose, and Throat Hospital and the West London Hospital. He practised privately in London, first in Eaton Square and later in the City. He had a very keen understanding of shipping affairs, and spent much of his time in the service of the Shipping Federation, of which he became chief medical officer. He was also medical adviser to the National Sea Training Schools, the Merchant Navy Officers' Pension Fund, and to various shipping companies. At the Joint Commission on the Hygiene of Seafarers, established by the International Labour Office and the World Health Organization after the second world war, he advised the British shipowners' delegation on medical matters, and he was a member of the Ministry of Transport's Committee for Revision of the Ship Captain's Medical Guide and Merchant Shipping Medical Scales. He served for a number of years on the Maritime Subcommittee of the B.M.A., and was at one time chairman of the special medical boards of the Ministry of Pensions. He was an honorary life member, lecturer, and examiner in first aid of the British Red Cross Society. During the early part of the second world war he was employed as a radiologist in the Emergency Medical Service, and he was medical officer to a London battalion of the Home Guard. He married Josephine Holman, and had three daughters and one son.

A. L. H. writes: It was during the latter part of the second world war that Eric Caldwell-Smith played a major part in the reorganization of the medical services of the Shipping Federation, at a time when it was called upon to administer the Merchant Navy pool and the need for a full-time medical service was becoming apparent. From small beginnings in the major ports he saw the service grow and develop under his guidance until it now comprises twenty-three full-time doctors, as well as some seventy part-time doctors in the smaller ports all over the country. He remained throughout its competent, efficient, but always sympathetic adviser and chief medical officer. Apart, however, from his expert knowledge of shipping affairs, he was also consultant to a number of companies, more especially in connexion with personal injury claims. He had a flair for this rather specialized type of work, and over the years accumulated a vast knowledge and experience. His medical reports were models of their type, and his opinion was greatly respected in both medical and legal circles. Moreover, his fairness and impartiality were such that he enjoyed the complete confidence of both shipowners'

and seafarers' organizations. Always a busy man, he loved his work and did not look forward to his retirement. For the last two years he was in failing health, but carried on even when his physical strength had almost gone. He was working in his city office right until the end. He was happily married for some forty years, and our sympathy is extended to his widow, son, and three daughters, who survive him.

J. B. BENNETT, M.B., Ch.B.

Dr. J. B. Bennett, who was in general practice at Hyde, Cheshire, for thirty-five years, died suddenly at his home there on September 12. He was 61 years of age.

John Barry Bennett was born at Hyde on June 17, 1898, the son of Dr. John Bennett, and was educated at Hyde Grammar School and at Willaston School, Nantwich. In 1914 he became a medical student at Manchester University, but his studies were interrupted by the first world war, on the outbreak of which he joined the Royal Field Artillery. He served in France, where he was wounded and taken prisoner. Although crippled by his wounds, he was able to resume his medical studies at Manchester on his return to England, and graduated M.B., Ch.B. in 1922. Subsequently he made a good recovery from his disablement. After graduation he was a house-surgeon with one of the teaching units at Manchester Royal Infirmary and an obstetrical officer at St. Mary's Hospital. He then joined his father in general practice at Hyde, where he was honorary secretary of the local Division of the B.M.A. from 1930 to 1945 and chairman in 1946–7 and again in 1956–7. He was a member of the Insurance Acts Committee and its successor, the General Medical Services Committee, from 1945 to 1951. He leaves a widow and two sons, one of whom, Dr. J. C. B. Bennett, had recently joined him in partnership.

J. K. writes: With the death of Dr. Barry Bennett the town of Hyde has lost another senior partner in a large family practice in eighteen months. It is in these small industrial towns, with their large proportion of craftsmen and craftswomen among their artisans who command a high standard of service, that the best family practices are to be found, and where the general practitioner finds the practice of medicine so satisfying and worth while. Dr. Barry Bennett so found it. His father, Dr. John Bennett, had practised in the town for upwards of fifty years, and the tradition of good family practice is continued by his own son, Dr. J. C. B. Bennett.

Dr. Barry Bennett was a first-class obstetrician, a quality which was of incalculable value in an industrial family practice. He was forthright in his attitude, but had a charm of manner which gave confidence to his patients and made him a very successful family doctor. His greatest contribution to medical administration was as a member of the local medical committee of the County Palatine of Chester and of the executive council. He was a member of the local medical committee for twenty-four years and was appointed secretary in 1946, and two years ago he became deputy vice-chairman of the executive council, holding both offices at his death. He was undoubtedly the linchpin of the National Health Service in Cheshire, where his knowledge of the Act and his ability in applying it to the needs of the people were invaluable. He was particularly happy in his home life, and took an active part in the social and cultural activities of the town. He served in the Home Guard in the second world war as a medical officer with the rank of major. He lived a very happy and useful life as a family doctor in an industrial community, and there are many families in Hyde who mourn with his widow and two sons.

Sir IAN HEILBRON, D.S.O., D.Sc., Ph.D., F.R.S.

Sir Ian Heilbron, professor emeritus of organic chemistry in the University of London, died in London on September 14, aged 72. Many of his contributions to medical science were of outstanding importance.

Ian Heilbron was born in Glasgow and educated at the High School there and at the Royal Technical College. After returning from service in the first world war, during which he won the D.S.O., he became professor of organic chemistry in turn at the Royal Technical College, Glasgow, at Liverpool, at Manchester, and at the Imperial College of Science and Technology. In 1949 he became the first director of the Brewing Industry Research Foundation. He was elected F.R.S. in 1931 and knighted in 1946.

A. H C. writes: Heilbron had, after spending two years with Hantzsch in Leipzig, returned to Glasgow in 1909 convinced of the future value of spectroscopy in organic chemistry, as is apparent from almost all his earlier publications. This belief permeated his pioneering work in connexion with the fat-soluble vitamins, and led nearly 25 years ago to the recognition of the photochemical conversion of ergosterol into vitamin D and the characteristic light-absorption of vitamin A. These extensive investigations, later furthered by other physical methods such as high-vacuum distillation and chromatography, for the introduction of which into Great Britain Heilbron was almost entirely responsible, provided the foundation on which were based many epoch-making advances in various laboratories in connexion with the steroids, polyenes, including the A vitamins, and the carotenoids.

During the second world war he played a leading part in the Anglo-American effort to unravel the chemistry and develop the industrial production of penicillin. From the medical and industrial standpoints an important outcome was the recognition of the plurality of the penicillins and of the possibility of controlling the production of individual members of the series by biosynthetic means. At the same time Heilbron's unbounded energy was being directed also to a variety of very different ends. Here mention may be made of his part in introducing D.D.T. as an insecticide to control disease-carrying insects which might otherwise have become a serious factor in war operations, and also of his intensive development of the chemistry of acetylenic compounds which eventually formed the basis of the industrial production elsewhere of vitamin A and carotene.

In university life he was, as occasion demanded, the brilliant organizer, the shrewd administrator, and above all the sympathetic professor who constantly had, in the most practical and direct manner, the welfare of each member of his department in mind. During the last twenty years of his life his incisive views were increasingly sought by industry, by Government services, and by science generally, both at home and abroad. In all these spheres his wisdom and balanced judgment were always obvious, but few can have fully realized the scrupulous care and tireless energy which went to form his apparently spontaneous opinions. In exceptional degree he had the gift of perceiving the basic features of any situation while putting less essential detail into proper perspective, and this perhaps is the thread running through all his scientific contributions over nearly 50 years. He was the outstanding example of one who could reach back in time to the "classical" period of organic chemistry but nevertheless always maintained himself in the forefront of research, and his influence was and still is much greater than even his massive contribution to scientific literature would indicate.

E. H. T. RUTHERFORD, M.B., Ch.B., F.R.C.S.Ed.

Mr. E. H. T. Rutherford, consultant venereologist at hospitals in Harrogate, York, and Goole, and assistant surgeon to Harrogate General Hospital, died in Harrogate on September 18, at the age of 56.

Eric Hugo Thomas Rutherford was born in Glasgow on March 11, 1903, the son of Dr. James Rutherford, and was educated at Glasgow Academy, Dollar Academy, and St. Andrews University, where he graduated M.B., Ch.B. in 1926. After qualification he held resident appointments at the North Lonsdale Hospital, Barrow-in-Furness, Harrogate General Hospital, and the Victoria Hospital for Children, Chelsea. In 1931 he took the F.R.C.S. of Edinburgh, and

subsequently held surgical appointments at Doncaster Royal Infirmary and the Victoria Infirmary, Blackpool, prior to becoming assistant surgeon at Harrogate General Hospital, a position which he held until his death. Prevented by illness from taking part in active service during the war, he became consultant venereologist to the Army at Catterick and to other Service units in Yorkshire. Owing to progressive disability from spondylitis, he was forced to reduce his surgical commitments, and at the conclusion of hostilities he retained his interest in venereology and became consultant in this specialty to the hospitals in Harrogate, York, and Goole.

Rutherford was honorary secretary of the Harrogate Division of the British Medical Association from 1933 to 1936, and a member of the Harrogate Medical Society. Outside his profession his chief interest was fishing. He is survived by his wife and two daughters.

T. V. P. writes: In mourning and commemorating Eric Rutherford it is impossible to write in general terms, as for so many his death has been a peculiarly personal grief. He courageously bore a long and painful illness and was well aware of his fate. He used to tell with wry humour how the Army authorities did not accept his statements and then were puzzled as to how to fit him on to their *x*-ray table. Naturally enough poor films were made which were difficult to interpret, and he kindly assisted his examiners to unravel the tangle. Very early in his career as a surgeon he knew before anyone else that he would have to confine his work to the shorter and less exhausting operations. With charming kindliness some years ago he gave his intestinal clamps to a colleague as a reward for some minor professional service. Here was very promising skill blasted by a cruel illness. An anaesthetist says he was the pleasantest surgeon of any to work with. Surgeons, especially the writer, knew him as the most agreeable, wise, and generous assistant, and only surgeons know what it is to have help from an assistant of equal status.

ALEXANDER CALLAM, D.S.O., T.D., M.D. F.R.C.S.Ed.

Mr. Alexander Callam, formerly honorary surgeon to the Victoria Hospital, Burnley, and consultant obstetrician and gynaecologist to the Burnley hospital group, died at his home in Edinburgh on September 20. He was 78 years of age.

Alexander Callam was born at Glenbuchat, Aberdeenshire, on October 4, 1880, and was educated at Robert Gordon's College and at Aberdeen University, where he graduated M.B., Ch.B. in 1903. Later in the same year he joined a partnership in Burnley, and soon built up the practice to be one of the best in the neighbourhood. He proceeded to the M.D. in 1907, and, always inclining to surgery, took the F.R.C.S.Ed. in 1926. He was awarded the D.S.O. in 1918 for his services as lieutenant-colonel in command of the East Lancashire Field Ambulance of the Territorial Army in France. The Territorial Decoration was also conferred upon him. A member of the British Medical Association for over fifty years, he was chairman of the Burnley Division in 1924–5 and president of the Lancashire and Cheshire Branch in 1935–6. He retired in 1952 and went to live in Edinburgh.

F. C. M. writes: Mr. Alexander Callam was for over forty years the central figure in the medical and surgical world of Burnley and district. A first-class surgeon, he held appointments at Burnley General and Burnley Victoria Hospitals and the Hartley Hospital, Colne. Equally skilled in obstetrics and gynaecology, his services were in constant demand, both in the special maternity hospitals and in general practice. Always full of energy, vitality, and enthusiasm, thorough and conscientious in every action, he was very popular among the general practitioners and the public. The buoyancy of his character brought with him an atmosphere of optimism, and there was nothing more heartening than to hear his Aberdeen accent as he arrived for any emergency at any hour. An untiring worker, he was a staunch supporter of and a pillar of strength to the local general practitioners and one of the finest all-rounders in any team. Our sympathy goes out to his widow and to his son, David, who is following his father's footsteps in Edinburgh.

Medico-Legal

ARSENIC SPRAYS FOR POTATOES

[From our Legal Correspondent]

A coroner's jury returned a verdict of death by misadventure on Mrs. Gwendoline Evans, of Bromyard, Herefordshire, on October 2 (*The Times*, October 3). Mrs. Evans, aged 38, and married to a farm labourer, became ill, together with her husband and five other people, after drinking water contaminated by an arsenical potato-spray. Three days later Mrs. Evans died.

Evidence was given at the inquest that the spraying equipment was faulty. The pump which pumped water from the supply tank into the spray tank allowed a feed-back into the main supply of the house at a rate of a gallon and a half (6.8 litres) every seven minutes. When tested, the water in the supply tank of the house contained 180 parts per million of arsenic. Traces remained in the tank even after it had been flushed out. The farmer stated that they had used the sprayer for seven years.

Dr. K. Valteris, a pathologist, said that Mrs. Evans died from "inflammation of the heart muscles, which might have been aggravated by arsenical poisoning." Quantities of arsenious oxide had been found in various organs in the body: Mrs. Evans had probably taken a total of about 2 gr. (0.13 g.). She might have survived the heart inflammation but for the poisoning.

The jury added to their verdict a rider "that these arsenical sprays should be prohibited altogether."

Within three days Messrs. Fisons Pest Control Ltd. announced (on October 5) that they were withdrawing from distributors all stocks of their arsenical spray "foliatox," which contains sodium and potassium arsenite, and that they would cease making it (*Journal*, October 10, p. 705). The product has been in use for 10 years for killing the haulms of potatoes at harvest time and against blight.

HEMP FROM BUDGERIGAR SEED

[From our Legal Correspondent]

The dry warm summer this year enabled Reuben Ritchie and John Luton, of Tiger Bay, Cardiff, to harvest 6 lb. (2.7 kg.) of Indian hemp from budgerigar seed grown on a disused allotment. The two men pleaded guilty on September 21 to being in unlawful possession of the drug, and were sentenced to nine months' imprisonment (*The Times*, September 22).

Indian hemp is defined by the Dangerous Drugs Act, 1951, as the dried flowering or fruiting tops of the pistillate plant known as *Cannabis sativa* from which the resin has not been extracted. This plant can usually be grown in England, but only very rarely does the English summer bring enough sun to ripen the fruiting tops and resinous glands. The Dangerous Drugs Act, 1951, and Regulations made under that Act strictly regulate the importing, manufacture, possession, or sale of specified drugs, of which Indian hemp is one. It is an offence for anyone to possess any of the specified drugs, unless he is one of the classes of persons authorized by the Statutory Regulations. Authorized persons include properly qualified medical practitioners, dentists, veterinary surgeons, pharmacists, persons in charge of certain laboratories, public analysts, and sampling officers.

It was stated on behalf of each of the accused that they were not members of a "sinister international drug ring."

One had taken to smoking hemp medicinally to relieve pain. The other had been given the drug as a very young man and had been unable to break the habit: he grew the drug only for his own use.

Indian hemp, shown by tests to be identical with the hemp in this case, featured in another case in Cardiff on October 5 (*The Times*, October 6). In this latter case a coloured man, also of Cardiff, who was addicted to the drug, pleaded guilty to the unlawful possession of 2 lb. 11 oz. (1 kg.) of Indian hemp, and was sentenced to 12 months' imprisonment.

Murder of Mental Patients Alleged.—Two doctors have been charged in West Berlin in connexion with the alleged murder of 26 mental patients in a Silesian hospital in 1945. Their names are given as Dr. G. Matthes and Dr. S. Benatzky.—*The Times*, August 21.

Universities and Colleges

UNIVERSITY OF EDINBURGH

At a graduation ceremonial on July 13 the following degrees and diplomas were conferred:

M.D.—*G. M. Carstairs, *P. N. Edmunds, *J. F. McHarg, *D. E. B. Powell, D. B. Scott, G. H. M. Thornton.

CH.M.—†H. D. Ritchie, †H. B. Torrance.

D.Sc.—*In the Department of Pure Science:* J. A. Loraine, Ph.D., M.B., Ch.B., M.R.C.P.Ed.

PH.D.—*In the Faculty of Medicine:* P. Bhuyan, M.B., B.S., R. B. Cross, M.B., B.S., T. J. Hulland, D.V.M., S. H. Ismail, M.B., Ch.B., I. Khan, M.B., B.S., G. R. Scott, M.Sc., A. E. Stuart, M.B., Ch.B., M.R.C.P.Ed.

M.B., CH.B.—Elinor W. Adam, A. C. A. Alexander, J. L. S. Alexander, K. Amatayakul, V. B. G. Amu, J. L. Anderton, R. W. Archibald, D. T. Baird, E. E. Barnard, D. G. D. Barr, D. S. G. Bath, P. W. D. Berry, J. L. Boak, F. A. Boddy, R. A. Bowie, Elizabeth M. W. Bradford, S. H. Brock, E. G. Buchanan, J. C. Burn, W. R. Cameron, Dorothy O. Campbell, M. Clare, R. L. Clark, F. Cockburn,‡ H. G. Coore, J. J. C. Cormack, A. B. Craddock, A. L. Crombie, G. K. Crompton, Christine E. J. Dandie, J. W. Delaney, M. J. Dell, A. W. Dellipiani, Mary E. Dewar, A. J. Dougall, A. Dumbreck, C. R. Dundas, H. P. Ferrer, A. Forsyth, Bernadette A. Gallagher, N. R. Galloway, P. F. Gibson, T. G. Girdwood, B. S. Goh, G. Gordon, Jessie Gordon, J. A. Gray, Alison F. Grieve, M. Grundy, A. Gunn, A. W. Harcus, L. J. Hastewell, R. D. Henderson, B. F. Heywood, Gillian Hindley, W. J. M. Hood, G. Horsburgh, A. W. Howarth, P. W. Kershaw, T. K. C. King, Mary Kinghorn, Edith McL. Lamont, Kathleen G. Large, D. Lees, Lorna J. Lees, J. G. Lemson, A. G. Livingstone, P. A. Loynds, J. M. Lynch, Gwendyth A. McAlpine, D. McCann, A. Macdonald, S. W. MacGregor, J. McKendrick, Eileen B. Mackenzie, Marjory G. McK. McKinnon, C. E. Mackintosh, M. S. F. McLachlan, T. K. Maclachlan, M. J. MacLean, C. McG. Mailer, C. M. Malone, D. N. S. Malone, A. G. Maran, G. R. Massarella, M. J. Mellor, G. T. Millar, Genevra M. Mitchell, T. O. Mulligan, R. Mulroy, Lilian E. Murchison, K. N. Murray, Margaret L. S. Murray, B. Newton, B. N. Panikker, Shirley R. Patterson, Margaret E. Pawson, J. K. Peden, Janet A. Peters, C. A. Phillips, Minnie W. Pollard, R. F. Pottinger, A. Ramsay, I. D. Ramsay, R. G. Rangecroft, A. K. Ravenscroft, Patricia M. Rebbeck, J. A. Redman, B. J. Ricci, Isobel A. Ritchie, I. W. P. Robb, R. M. Rowan, C. V. Ruckley, D. M. Scruby, E. R. Seiler, S. Selwyn, B. W. Serpell, W. I. H. Shedden, Ann I. Simpson, C. A. Simpson, M. M. Simpson, R. D. C. Sinclair, R. A. Sleet, D. J. C. Sneddon, R. T. Steele, R. E. Steward, A. Tejavej (formerly Chuangphanich), I. C. Thomson, G. K. H. Tsang, A. M. Tulloch, J. G. Turnbull, F. W. Turner,‡ J. H. Turner, E. E. Udoh, Anne M. Urquhart, D. D. Walker, Jean G. Walker, Joan Wallace, W. L. White, J. Williamson, Catharine D. Wilson, K. M. Wood, D. G. Wray, A. K. Zealley.

B.Sc.—*In Department of Pure Science:* G. Philp, M.B., Ch.B. (with second-class honours in bacteriology).

DIPLOMA IN PUBLIC HEALTH.—A. McI. Anderson, Anne J. Anderson, T. G. Behan, G. M. A. H. Bernard-La Pommeray, C. H. James, V. K. Kyaruzi, W. E. Laufer, J. A. MacDougall, Marian F. Natkanski, G. S. C. Nzegwu, J. Oliver, Sheila G. Quain, I. F. Ralph, A. Watt.

DIPLOMA IN PSYCHIATRY.—A. H. C. Sinclair-Gieben.

DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—M. F. Azam, K. S. Bedi, S. K. Datta, E. E. Inyang, G. C. Irvine, K. V. S. Krishna Das, M. S. Mahuli, B. Mittra, D. Ogston, N. K. Purushothaman.

*Commended for thesis. †Gold medal for thesis. ‡With honours.

The following scholarships, etc., were awarded in the Faculty of Medicine: *Ettles Scholarship, Leslie Gold Medal in Medicine, Mouat Scholarship in the Practice of Physic, Murchison Memorial Scholarship in Clinical Medicine, Beaney Prize in Anatomy and Surgery, Keith Memorial Prize in Systematic Surgery,* and *Annandale Gold Medal in Clinical Surgery,* J. H. Turner. *Scottish Association for Medical Education of Women Prize* and *Dorothy Gilfillan Memorial Prize,* Lilian E. Murchison. *Chiene Medal in Surgery,* H. B. Torrance. *Buchanan Scholarship in Obstetrics and Gynaecology* and *Murdoch Brown Medal in Clinical Medicine,* A. W. Dellipiani. *James Scott Scholarship in Obstetrics and Gynaecology,* D. T. Baird. *Lawson Gifford Prize in Obstetrics and Gynaecology,* Margaret L. S. Murray. *Wightman Prize in Clinical Medicine,* M. J. MacLean. *Royal Victoria Hospital Tuberculosis Trust Gold Medal,* G. R. Massarella. *Conan Doyle Prize,* M. J. Dell. *Graduate Research Fellowships,* Jean-Marie de Margerie, R. A. Harkness, J. McE. McI. Neilson, Elspeth M. Russell. *Graduate Research Scholarships,* Phyllis M. Fulton, J. T. Hamilton, W. J. Irvine, R. Lévy, I. W. Sutherland. *Graduate Travelling Scholarships,* A. E. Stuart, J. H. Bowie. *Gunning Victoria Jubilee Prize in Materia Medica,* E. W. Horton. *Gunning Victoria Jubilee Prize in Pathology,* W. J. Irvine. *Lauder Brunton Medal and Prize in Pharmacology and Therapeutics,* G. W. K. Donaldson. *Greig Medal for Tropical Medicine,* B. Mittra and D. Ogston (equal). *Ash Prize for Oral Pathology,* J. F. Gould. *Lawrence Poole Prize in Rehabilitation after Poliomyelitis,* G. W. A. Dick and D. M. S. Dane (jointly).

UNIVERSITY OF DURHAM

In Congregation on September 26 the following degree and diplomas were conferred:

D.D.Sc.—C. H. Tonge, M.B., B.S., B.D.S.

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—Jean Hayek, T. M. Maguire, C. Protheroe.

SOCIETY OF APOTHECARIES OF LONDON

The following candidates, having completed the final examination, have been granted the diploma of L.M.S.S.A.:

J. J. O'Donnell, C. Dunster, A. M. Sherrington, G. R. Graham, D. H. Hamilton, M. G. Royle, T. A. Thorburn, J. C. Roberts, M. J. Streule, S. H. N. Pratt, B. Malek, R. G. Holmes, P. J. A. V. Willems, H. Bayoumi, A. S. Horniblow, M. H. Marsh, P. Williams, R. E. Kendell, I. K. Dajani, J. A. Bushman, S. L. Geoghegan, R. K. Elias.

The Diploma in Mastery of Midwifery has been awarded to D. L. Sladden.

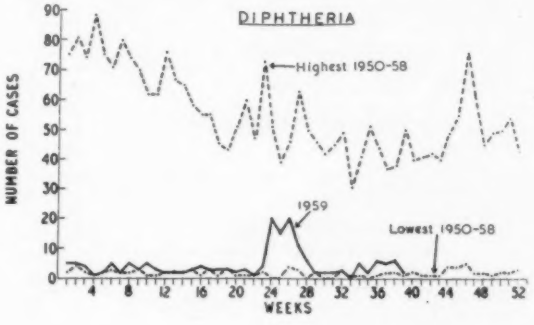
Vital Statistics

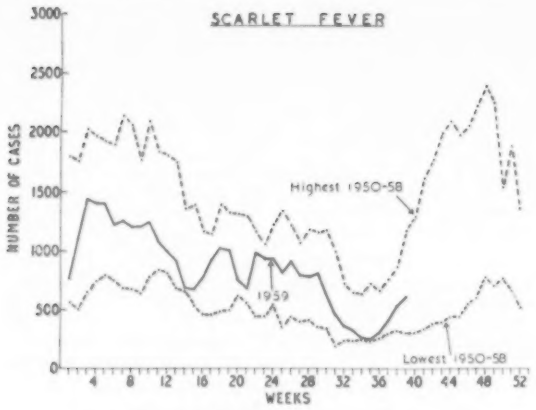
Gonorrhoea in Edinburgh

In 1958 a higher incidence of gonorrhoea was recorded in Edinburgh than in recent years, according to the Annual Report of the city's Public Health Department. Cases numbered 730 (males 500, females 230), compared with 688 in 1957 and 487 in 1956. The author of this part of the report, Dr. ROBERT LEES, says there appears to be an undetected reservoir of infection in the population, and many apparent "cures" are not complete. Gonorrhoea is becoming partially resistant to penicillin; moreover, many patients disappear as soon as symptoms are relieved. "There is some danger, too, that busy doctors may prescribe one of the many antibiotics or some other convenient product of the persuasive pharmaceutic industry rather than arrange a fuller investigation." See also leading article in last week's *Journal*, October 10, p. 685.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.





Week Ending October 3

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Sept. 26	Week Ending Oct. 3
Acute Poliomyelitis		
Lancashire	4	7
Leigh M.B.	0	3
Yorkshire West Riding	3	6
Leeds C.B.	2	4
Dysentery		
Lancashire	111	100
Liverpool C.B.	22	19
Swinton and Pendlebury M.B.	26	41
London	62	55
Northamptonshire	4	11
Northampton C.B.	3	11
Surrey	17	17
Croydon C.B.	9	11
Warwickshire	25	45
Birmingham C.B.	16	9
Coventry C.B.	8	33
Yorkshire East Riding	62	26
Kingston upon Hull C.B.	49	18
Yorkshire West Riding	83	88
Barnsley C.B.	32	33
Leeds C.B.	25	25
Glasgow	104	222
Edinburgh	9	26
Food-poisoning		
Lancashire	85	76
Liverpool C.B.	30	21
Diphtheria		
London	3	2
Islington	1	2
Cerebrospinal Fever		
Glasgow	3	16
Acute Infective Encephalitis		
Durham	1	3
Gateshead	1	3
Durham M.B.	0	1
Diarrhoea and Enteritis in Infants up to 2 Years		
Belfast C.B.	15	15
Dublin C.B.	60	31
Dublin County	11	3

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending September 26 (No. 38) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	6	3	1	0	2	2	0	2	0	3
Dysentery	529	62	195	1	2	410	63	169	12	
Encephalitis, acute	3	0		0		5	0		0	
Enteric fever:										
Typhoid	4	2	1	3		6	3	1	1	1
Paratyphoid	18	0	0	0	8(B)	5	3	1(B)	1	3(B)
Food-poisoning	343	34	22	2		369	41	21	1	
Infective enteritis or diarrhoea under 2 years				18	72				14	44
Measles*	687	20	14	20	14	1,470	109	26	8	37
Meningococcal infection	17	1	9	1		9	2	8	0	
Ophthalmia neonatorum	29	1	5	0		17	3	2	0	
Pneumonia†	132	10	109	2		175	11	90	0	1
Poliomyelitis, acute:										
Paralytic	22	3	0	1		48	2	17	1	10
Non-paralytic	13	2	2			31	1			
Puerperal fever§	187	30	7	1		226	40	12	1	
Scarlet fever	531	37	80	14	15	434	24	61	26	17
Tuberculosis:										
Respiratory	440	61	56	16		458	44	62	17	
Non-respiratory	48	2	8	2		62	6	14	4	
Whooping-cough	784	41	79	10	29	718	36	69	47	10

DEATHS	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	0	0	0	0	0	0	0	0	0	1
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	3	0	1	1	2	6	1	0	0	0
Influenza	5	0	0	1	0	3	0	0	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				1	0		
Pneumonia	334	28	14	14	0	304	19	4	7	9
Poliomyelitis, acute	3	1		0	0	1	0	1	0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	50	1	2	1	3	46	3	4	1	2
Non-respiratory		0	1	0	0		1	0	0	0
Whooping-cough	0	0	0	0	0	2	0	0	1	0
Deaths 0–1 year	260	27	33	8	8	298	33	21	3	9
Deaths (excluding stillbirths)	7,931	662	523	103	108	7,889	621	443	89	130
LIVE BIRTHS	14,046	1263	887	259	313	13,725	1178	969	204	353
STILLBIRTHS	296	26	16			331	33	18		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

B.M.A. Scientific Exhibition, 1960.—The Annual Scientific Meeting of the British Medical Association is to be held in Torquay next year from June 20 to 24, and those who wish to exhibit at the Scientific Exhibition should apply for a stand as soon as possible. In view of the site available, the Exhibition will necessarily be smaller than in recent years, and it is requested that each exhibit should so far as possible be self-explanatory and should not require the presence of a demonstrator. Awards of certificates of merit will be made to the exhibits judged to be of the highest standard of presentation and of the highest scientific merit and originality. Application forms for space at the exhibition are obtainable from the Secretary, B.M.A. House, Tavistock Square, London, W.C.1, the closing date for applications being December 31.

Wellcome Trust Grants.—Among the medical research grants totalling over £400,000 made by the Wellcome Trust during the 12-month period ended August 31, 1959, were the following:

University of Cambridge.—Up to £120,000 to extend research accommodation in the biochemistry department, and up to £60,000 to provide new laboratories for the department of radiotherapeutics. *Royal Infirmary, Manchester.*—Up to £30,000 to provide a metabolic research unit. *University and City Hospital, Edinburgh.*—Up to £28,000 to build a respiratory diseases research unit. *University of Oxford.*—Up to £11,500 to provide an ultracentrifuge and microelectrophoresis equipment in the Sir William Dunn School of Pathology, and up to £3,000 to provide a recording spectrophotometer in the department of inorganic chemistry. *Medical Research Council.*—Up to £9,500 to provide an electron microscope for use in the Institute of Ophthalmology, University of London. *Worshipful Society of Apothecaries of London.*—Up to £3,600 to establish a Research Fellowship in the history of medicine and pharmacy. *Society for Study of Fertility.*—Guarantee of up to £2,000 to establish a *Journal of Reproduction and Fertility*. *University of East Africa, Makerere College.*—Up to £12,500 to provide a mobile laboratory and an animal-house for the physiology department. Grants to individuals for research assistance or expenses totalled £42,500, and 116 Wellcome Research Travel Grants were awarded at an over-all cost of £22,000.

Postgraduate Travelling Fellowships.—The British Postgraduate Medical Federation invites applications from registered medical or dental practitioners for a limited number of Postgraduate Travelling Fellowships, details of which were given in the *Journal* of October 10, advertisement page 64. The Fellowships will normally be tenable for one year from September or October, 1960, and applications must be submitted before November 30, 1959, to the Assistant Director of the Federation, Central Office, 18, Guilford Street, London, W.C.1.

Fewer Waiting.—About 25% of the elderly chronic sick in England and Wales whose names are on hospital waiting-lists are probably already in hospital. The King Edward's Hospital Fund for London reached this conclusion after studying the figures for 10 hospital groups in a metropolitan hospital region. In its report, *Hospital Personal Aid Service for the Elderly*, the Fund states: "We feel that there is enough evidence to cause serious misgivings, and if every hospital group were to make similar investigations into the cases on their waiting-list . . . many elderly people would have more practical help than they have at present."

Moynihan Chirurgical Club Jubilee Meeting.—Surgeons from here and overseas gathered in Leeds Civic Hall to pay homage to the memory of Lord Moynihan at the fiftieth anniversary banquet of the Club, which he founded to foster the progress of surgery, and to encourage friendship between surgeons, at home and abroad. Responding to the toast to his memory, his son, Lord Moynihan, recalled that before the Club's foundation there was a striking lack of cohesion between members of the profession. By bringing surgeons into such a fraternity the profession benefited enormously from the pooling of experience and the breaking down of prejudices. In this way, continued Lord Moynihan, quoting his father's own words, he helped surgeons to realize that "we were not competitors but comrades, each working with the other against the common enemy—disease." The toast of Berkeley Moynihan was jointly proposed by the president of the Club, Professor Digby Chamberlain, Mr. George Armitage, and Dr. Alton Ochsner, past president of the American College of Surgeons, while the toast of the Moynihan Chirurgical Club was proposed by Sir Ernest Finch. Mr. Robert Cooke, who was retiring after 10 years as secretary, was presented with a silver salver. Representatives of other surgical clubs were present, and had taken part in the two-day scientific meeting which preceded the banquet. Visitors from overseas included Professor Mallet Guy (Lyons), Professor A. C. Brom (Leyden), Professor E. Dahl-Iverson (Copenhagen), Professor I. Boerema (Amsterdam), and Professor R. Geissendorfer (Frankfurt).

Red Cross Founder's Centenary.—On October 14, as part of the "Swiss Fortnight" programme, Lady Limerick unveiled at Park Lane House a wax model of Henri Dunant, the Swiss businessman who founded the Red Cross. It is now on display at Madame Tussaud's.

Dunant, who was seeking a business concession from the French Emperor Napoleon III, was an unwilling witness of the battle of Solferino (1859), between the armies of France and Sardinia and that of Austria. The French victors lost 11,600 men, the vanquished 22,000, largely as a result of the devastating effect of modern firearms on the close formations, the intense heat, and lack of water during the 15-hour battle. Dunant was so appalled by the carnage that in 1862 he published *A Memory of Solferino*, which included a sketch of his ideas for the care of the wounded, and by 1864, largely through his efforts, a permanent international committee had been set up, the first Geneva convention signed, and a red cross on a white ground, the Swiss flag in reverse, adopted as the emblem of protection. The model of Dunant has been made by Bernard Tussaud, Madame Tussaud's great-great-grandson, from photographs similar to the one shown here, and it will be on permanent display in a group of "pioneers of human endeavour" which includes Dr. Livingstone and Nurse Edith Cavell.

Medical Research in Scotland.—The Secretary of State for Scotland has appointed five new members to the Advisory Committee on Medical Research in Scotland to take the place of five retiring members. The new members are: Professor J. H. F. Brotherston (department of public health and social medicine, Usher Institute, Edinburgh), Professor J. N. Davidson (department of biochemistry, Glasgow University), Professor R. B. Hunter (department of pharmacology and therapeutics, Queen's College, Dundee), Professor Alexander Macdonald (department of bacteriology, Aberdeen University), and Professor G. L. Montgomery (pathology department, Edinburgh University).

Royal Medical Benevolent Fund.—At the annual general meeting of the Fund held on September 30 the following honorary officials were elected: President, Sir Henry Tidy; treasurer, Mr. F. A. Juler; secretary, Dr. T. Anwyl-Davies.

Edinburgh University.—The Lawrence Poole Prize in Rehabilitation after Poliomyelitis has been awarded jointly to Dr. G. W. A. Dick and Dr. D. M. S. Dane.

COMING EVENTS

Postgraduate Course in Orthopaedics. — One-day instructional course in orthopaedics at the Royal College of Surgeons, October 22 at 10 a.m. Tickets (attendance 10s., lunch and coffee 10s.) and further details from the secretary, British Orthopaedic Association, 47, Lincoln's Inn Fields, London, W.C.2.

Glasgow Medical Graduates (Male) Midland Association.—Annual dinner, Queen's Hotel, Birmingham, October 30. Tickets from Dr. J. R. Preston, M.O.H., Council House, Sutton Coldfield.

Society for Study of Addiction.—Annual dinner, Talbot Restaurant, 64, London Wall, E.C.2, October 19, 7 p.m. Guest speaker, Sir Ernest Gowers: "Cliché Addiction." Details from Mr. W. R. Bett, 11, The Avenue, Bedford Park, London, W.4.

World Clean Air Conference.—National Society for Clean Air Diamond Jubilee, Seymour Hall, W.1, October 20–23. Details from the Society, Palace Chambers, Bridge Street, London, S.W.1. (TRA 6838/9.)

Liverpool University.—A course of 10 Tuesday lectures on "The Development and Use of Modern Drugs," which began on October 13, will be held at 7.30 p.m., in the Medical School, Ashton Street (off Brownlow Hill), Liverpool. Details from the Director of Extra-Mural Studies, 9, Abercromby Square, Liverpool, 7.

College of General Practitioners, North London Faculty Meeting.—Dr. Norman Whittaker: "Use and Abuse of Investigations," North Middlesex Hospital, Silver Street, Edmonton, N.18, October 27, 8.15 p.m. Refreshments. Please notify Dr. P. Hopkins, 249, Haverstock Hill, Hampstead, N.W.3, if attending, by October 24.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Sunday, October 18

●Medical World.—At Victoria Halls, Bloomsbury, London, W.C., 10 a.m., Second Medical World Conference.

Monday, October 19

Edinburgh University.—At Anatomy Lecture Theatre, University New Buildings, Teviot Place, 5 p.m., Inaugural Lecture by Professor K. W. Donald: Research and Clinical Medicine.

Institute of Neurology.—5.30 p.m., Dr. J. W. Magladery (Baltimore): Certain Neurophysiological Studies of Ageing.

London University.—At Birkbeck College, Malet Street, W.C., 6 p.m., special university lecture in psychology by Professor E. G. Boring (Harvard): Pattern of Modern Psychology—(i) Psychology of the History of Science.

Postgraduate Medical School of London.—4 p.m., Dr. F. Gardner: Some Aspects of Coronary Artery Disease.

Royal Free Hospital School of Medicine (London University).—5.30 p.m., Professor H. Dowling (Illinois): Long-term Treatment of Bronchiectasis and Chronic Bronchitis with Antibiotics.

St. Andrews University.—At Demonstration Room, Department of Medicine, 4 p.m., Dr. K. G. Lowe: Cardiac Catheter as a Tool in Cardiology.

Society for the Study of Addiction.—At Talbot Restaurant, 64, London Wall, E.C., 7 for 7.30 p.m., annual dinner. Guest speaker, Sir Ernest Gowers: Cliché Addiction.

Tuesday, October 20

Belmont Hospital Clinical Society.—8 p.m., Dr. W. L. Neustatter: Diminished Responsibility in Murder.

British Postgraduate Medical Federation.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor R. H. S. Thompson: Biochemistry of Multiple Sclerosis.

Ilford Medical Society.—At King George Hospital, Ilford, 8.45 p.m., discussion on Report of Maternity Services Committee (Cranbrook Report). Chairman, Rt. Hon. Earl of Cranbrook. Speakers, Professor W. C. W. Nixon, Dr. G. L. Kennedy, and Dr. J. D. Kershaw. Members of Stratford Division, B.M.A., are invited.

Institute of Dermatology.—5.30 p.m., Dr. C. D. Calnan: Allergic Reactions of the Skin.

Leeds Neurological Sciences Colloquium, 1959-60.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Dr. J. B. Cook: Relationship of Spinal Cord Damage to Cervical Spinal Injury.

●Liverpool University: Department of Extra-Mural Studies.—At Medical School, Ashton Street, 7.30 p.m., Dr. J. B. Roberts: Actions of Drugs on the Central Nervous System, with Special Reference to Hypnotic Drugs.

Postgraduate Medical School of London.—4 p.m., Dr. E. H. Belcher: Properties of Radiation.

St. Andrews University.—At Physiology Department Lecture Theatre, Queen's College, Dundee, 5 p.m., Dr. J. S. S. Stewart: Cyto-genetical Techniques in the Investigation of Human Intersexes.

Society for the Study of Addiction.—At Medical Society of London, 11, Chandos Street, W., 8 p.m., Symposium on the Influence of Drugs on Literary Imagination. Opener, Professor Douglas Hubble.

South-west London Medical Society.—At Bolingbroke Hospital, 8.45 p.m., Mr. A. M. Desmond: Peripheral Vascular Disease.

Wednesday, October 21

Eugenics Society.—At Rooms of Royal Society, Burlington House, Piccadilly, W., 5.30 p.m., Miss Eileen M. Brooke, M.Sc., D.P.A.: Mental Health and the Population.

Harveian Society of London.—8.15 p.m., Buckston Browne Prize Essay by Dr. R. N. Tattersall: Clinical Significance of Tiredness.

Institute of Dermatology.—5.30 p.m., Dr. H. Haber: Histology of Normal Skin.

Institute of Diseases of the Chest.—5 p.m., Mr. Vernon C. Thompson: Diaphragmatic Hernia.

Institute of Urology.—4.30 for 5 p.m., Mr. D. E. H. Phillips: Enlarged Prostate: Pathological Considerations.

Postgraduate Medical School of London.—2 p.m., Dr. H. E. de Wardener: Renal Function.

Royal College of Surgeons of Edinburgh.—3.30 p.m., Mr. M. F. Nicholls: Behaviour of Tumours.

Royal Institute of Public Health and Hygiene.—3.30 p.m., Mr. T. L. Mackie, M.I.N.A.: Clean Air Act, 1956, Its Implementation and Application to Vessels.

St. Andrews University.—At Demonstration Room, Department of Medicine, 2.30 p.m., Professor I. G. W. Hill and Staff: Some Aspects of Electrocardiography, including Intracardiac Leads.

Thursday, October 22

British Postgraduate Medical Federation.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. P. B. Bradley: Neurophysiology of Consciousness.

Institute of Dermatology.—5.30 p.m., Dr. F. F. Hellier: Rehabilitation of the Skin Patient.

London University.—At Birkbeck College, Malet Street, W.C., 6 p.m., special university lecture in psychology by Professor E. G. Boring (Harvard): Pattern of Modern Psychology—(ii) Genesis of Modern Psychology.

Royal College of Surgeons of England.—4.15 p.m., Arnott Demonstration by Dr. S. Engel: Evolution of the Mammalian Lung.

Royal Eye Hospital.—3.30 p.m., Dr. T. H. Whittington: The Reduced Eye.

St. Andrews University.—At Physiology Department Lecture Theatre, Queen's College, Dundee, 5 p.m., Professor Andrew W. Kay: Some Surgical Experiments in Duodenal Ulcer.

St. George's Hospital Medical School.—5 p.m., Sir Paul Mallinson: demonstration in psychiatry.

University College London.—At Anatomy Theatre, Gower Street, W.C., 1.15 p.m., Professor L. S. Penrose, F.R.S.: Human Chromosomes.

Friday, October 23

Edinburgh University.—At Anatomy Lecture Theatre, University New Buildings, Teviot Place, 5 p.m., Inaugural Lecture by Professor R. B. Fisher: Biochemistry in Relation to Medicine.

●Institute of Dermatology.—5.30 p.m., Dr. Brian Russell: clinical demonstration.

Institute of Diseases of the Chest.—5 p.m., Dr. N. Lloyd Rusby: clinical demonstration.

Institute of Laryngology and Otology.—4.30 p.m., Annual Address by Mr. C. P. Wilson: Vasomotor Catarrhs of the Nose.

Institute of Neurology.—4.45 p.m., Dr. G. D. Dawson: Investigations on Sensory Inflow.

Manchester University.—5.15 p.m., Lloyd Roberts lecture by Professor A. C. B. Lovell, F.R.S.: Structure of the Universe.

Postgraduate Medical School of London.—(1) 10 a.m., Professor R. S. Pilcher: Surgical Treatment of Angina Pectoris. (2) 4 p.m., Dr. M. D. Milne: Disorders of Potassium Metabolism.

Royal Society of Health.—At Council Chamber, Town Hall, Darlington, 10 a.m., Dr. J. Tregillus: Coronary Heart Disease and Possible Preventive Measures.

Sunday, October 25

Haemophilia Society.—At General Hospital, Birmingham, 3.30 p.m., general meeting. Address by Dr. M. J. Meynell.

Manchester University: Faculty of Medicine and College of General Practitioners: North-west England Faculty.—At Theatre I, Clinical Sciences Building, York Place, 11 a.m., Professor W. I. C. Morris: Obstetrics.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Hurwood.—On October 4, 1959, at Wanstead Hospital, London, E., to Joyce, wife of Hubert Anthony Hurwood, M.B., B.S., D.Obst.R.C.O.G., a daughter—Gillian Wendy.

DEATHS

Bashford.—On August 27, 1959, at Queen Elizabeth Hospital, Birmingham, Guy Rosslyn Bashford, M.B., Ch.B., of Ranelagh House, Tamworth Road, Sutton Coldfield, Warwicks.

Bennett.—On September 12, 1959, at Stockley Place, Hyde, Cheshire, John Barry Bennett, M.B., Ch.B., aged 61.

Gilmore.—On September 15, 1959, at Chalmers Hospital, Edinburgh, Haldane Carson Gilmore, L.R.C.P.&S.I. and L.M., of Cooldorragh, Baterno, Midlothian, aged 70.

Leaver.—On September 14, 1959, Robert Henry Leaver, M.R.C.S., L.R.C.P., of 35, Palace Court, London, W.

Lees.—On September 12, 1959, at Salisbury General Infirmary, Robert Norman Lees, M.C., M.B., Ch.B., of Estyard, Fontmell Magna, Shaftesbury, Dorset, aged 44.

Lowe.—On September 18, 1959, at the Manor House Hospital, Golders Green, London, N.W., Charles Edwin Maximilian Lowe, M.B., Ch.B., Lieutenant-Colonel, R.A.M.C. and R.A. (T.F.), retired, late of Harley Street, London, W.

Silas.—On September 14, 1959, at Littlehampton, Sussex, Walter Biscombe Silas, M.R.C.S., L.R.C.P., of 13, Maltravers Drive, Littlehampton, late of Blackheath, London, S.E., aged 85.

Wilkinson.—On September 13, 1959, at Madeira, Stephen Harold Wilkinson, M.D., late of Bradfield, Berks.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Decidual Bleeding during Pregnancy

Q.—*For how long can a woman have the monthly cycle while she is pregnant? What is the pathology of the condition, and does it require any treatment?*

A.—Decidual bleeding from the cavity of the uterus does occur during pregnancy at the times of the normally suppressed periods. It is usually less in amount than a normal period. It is commonest at the 4th week, less common and nearly always less in amount at the 8th week, and rare at the 12th week. Such bleeding occurs despite the continuing hormonal support given to the decidua by the pregnancy, and the reasons for this are unknown. It may recur cyclically until the cavity of the uterus is obliterated at the 4th month by fusion of the decidua capsularis with the decidua vera. An exception would be if the patient has a double uterus, but pregnancy in one-half of such a uterus is not usually accompanied by cyclical decidual bleeding. Some of the patients with recurring bleeding in pregnancy are later found to have a low-lying placenta, while in others the shed placenta is later seen to be circumvallate in type, but in these cases the bleeding is not truly cyclical. Clinically, decidual bleeding requires no treatment. The important points are to make sure that the haemorrhage really is cyclical in timing, and to exclude complications of pregnancy, such as abortion, and local organic causes, such as cervical polyp or erosion.

Calcinosis and Marriage

Q.—*A woman of 24 who wants to get married has for the past ten years suffered from calcinosis which is now fairly marked, particularly in her hands, despite all treatment, including a bilateral sympathectomy. Is this disease transmissible? What effect might pregnancy have on her condition?*

A.—It is presumed that the question refers to the local form of calcinosis associated with acrosclerosis. There is no evidence that this condition is transmissible. There have been claims that it may be relieved or arrested by steroid therapy, in which case the pregnant state—with raised plasma levels of adrenal corticoids—might be expected to have, if anything, a beneficial effect.

Avoiding Cerebral Accidents

Q.—*What symptoms warn an elderly patient of an impending cerebral accident, and what can be done to prevent it?*

A.—There are no specific symptoms which warn an elderly patient of an impending cerebral accident. If, however, a patient has already had one "accident" he may recognize a recurrence of the type of headache, giddiness, or "heaviness" which he experienced previously, and as a result he may be warned of a second accident if this is heralded in a similar way.

The symptoms may include headache—not always occipital—"heaviness," giddiness, nausea and vomiting, "funny sensations" in the head, and even occasionally pain in the chest. None of these, however, can be regarded as specific, and some patients recall no symptoms at all. They remember nothing between full health and recovery of consciousness after the stroke.

There is little that can be done to prevent a cerebral accident, but general principles should be observed. These include avoidance of obesity—especially when associated with hypertension—and of all types of excess. There should be moderation of food and drink and of emotional scenes of any kind. Similarly, while encouraging normal activity among elderly persons, it is well to avoid great physical strain, especially immediately after a heavy meal. Auricular fibrillation should be controlled to prevent those accidents due to small cerebral emboli, and hypotensive drugs should be considered in patients with severe hypertension.

Aerophagy

Q.—*What advice should be given to a patient suffering from aerophagy?*

A.—Practically all the gas in the intestine in normal people is air that is swallowed. This is often done unconsciously while gulping fluids or sometimes by chewing food. It is not uncommon for some people to burp after the end of a meal and expel any excess air that has been swallowed. Some individuals, particularly if there is a background of nervous tension, will develop a nervous habit of swallowing air, often by little swallowing movements, and then proceed to try to bring it up. In so doing they occasionally swallow much more air, and a vicious circle is induced. The patient should make every effort to try not to bring up this wind more often than once after a meal. Often lying down on the left side after a meal may enable gas to pass from the stomach into the intestine, and so reduce discomfort. One discomfort is aggravated by associated constipation, and dietary assistance for the bowels may be needed. This aggravation is due to gas remaining in the colon and giving rise to distension and discomfort, which in turn may induce more air-swallowing.

Drugs and Driving

Q.—*Which drugs, and at what dosage, make it inadvisable for a patient receiving them to drive his own car?*

A.—It is, of course, difficult to reply to this question with precise indications of dose, but otherwise the drugs which make it inadvisable for a patient to drive his own car are those which slow his reaction time. The one which has been investigated with care and on which precise information is available is alcohol. Alcohol does not interfere with routine driving movements, but it diminishes the accuracy of judgment and slows the time at which a reaction follows a stimulus. Evidence on these points is given in the papers by K. Bjerver and L. Goldberg[1] and G. C. Drew *et al.*[2]

Other drugs which slow reaction time are the barbiturates, such as phenobarbitone and butobarbitone, methylpentynol, the antihistamines, and substances like pethidine. The extent to which these affect different individuals varies, some being much less affected in driving than others. Moreover, it is likely that the amount of any of these drugs which a given individual can take without affecting his performance will vary at different times. It appears to be particularly dangerous to combine these drugs with alcohol, as this affects the extent and rapidity with which they are absorbed.

Some of the antihistamines are much more prone to cause confusion than others, but again in occasional individuals the effect of those which are less likely to cause confusion is greater than would be expected. Thus it may be said that all the depressant drugs are likely to increase the risk of driving accidents, though there is as yet no clear evidence about the tranquillizing agents.

References

1 Bjerver, K., and Goldberg, L., *Quart. J. Studies on Alcohol*, 1950, **11**, 1.
2 Drew, G. C., Colquhoun, W. P., and Long, H. A., *Brit. med. J.*, 1958, **2**, 993.

NOTES AND COMMENTS

Anuria After Concealed Accidental Haemorrhage.—Dr. D. O'Sullivan (Blackburn) writes: I was most interested to read your expert's answer to the question on treatment of anuria following accidental haemorrhage (*Journal*, August 22, p. 255). It struck me, however, that more emphasis could wisely be placed on what should be considered the most important aspect of treatment of

anuria in such circumstances—i.e., the early evacuation of the uterus. This latter procedure is an essential curative step, as it removes the nocuous factor or factors primarily responsible for exciting the renal pathological process. In most cases, early evacuation of the uterus implies performing a caesarean section, as in the early stages of anuria in accidental haemorrhage the cervix is almost invariably undilated. It may appear superfluous doing a laparotomy at such an early stage, especially when the ostensibly immediate fruits of surgery are a stillborn foetus, but better a scar in the lower segment than multiple scars in the kidneys. What must be grasped is that the early stages of this renal complication are reversible. Rupturing the membranes and waiting hours or days for spontaneous uterine evacuation is tantamount to ensuring that the irreversible stage of renal necrosis becomes established. Then, of course, no matter what therapy is instituted in an effort to maintain the constancy of the *milieu interne*, the prognosis is extremely grave. The essential physiopathological process underlying renal parenchymal necrosis is hitherto ill understood. But certain it is that the basic disturbance is contained within the uterus. The severity in degree of renal disease is directly proportional to the time interval involved between onset of anuria and evacuation of the uterus. For every hour one waits for delivery another nail goes into the parturient's coffin. Remove the cause by early evacuation of the uterus and cure. Procrastinate and kill.

Our Expert replies: The question and answer which have attracted this comment were concerned with the treatment of anuria and not of accidental antepartum haemorrhage. Treatment of the latter necessitates consideration of many factors such as maternal age and parity, the condition of the foetus, the degree of maternal shock, and the presence of blood-coagulation defects; it cannot profitably be determined merely by the possible occurrence of what is now its rarest complication—renal cortical necrosis. In a hospital serving a community similar to that in Blackburn there were, during the last 10 years, 684 cases of accidental antepartum haemorrhage. The severity of the cases can be judged by the fact that the foetal mortality was 30% (24% babies being dead *in utero* when the patient was admitted). In approximately half the cases there was a significant amount of concealed haemorrhage, and in the more serious of these there was haematological evidence of a blood-coagulation defect in 30%. Two mothers died, one from primary shock within a few minutes of admission, and one from post-partum and retroperitoneal haemorrhage associated with blood-coagulation failure. Significant and worrying oliguria, persisting beyond the phase of circulatory depression, occurred only twice in this series, both times in women delivered within 12 hours of admission. It was not fatal, and both patients showed normal renal function tests three months later. Only 30 of the 684 women (4%) were delivered by caesarean section, mostly for the sake of the foetus or for obstetrical reasons other than the placental separation. It would be of interest to know the basis for Dr. O'Sullivan's assertion that the degree of renal damage is directly proportional to the interval between the onset of anuria and the time of delivery. This and allied considerations, such as the prophylactic value of immediate blood transfusions, are matters on which scientific information is lacking. It seems probable that the arrest of the cortical blood supply occurs at the onset of placental detachment with its accompanying shock, and there is evidence that, unless the ischaemia ceases within approximately two hours, the affected area of renal cortex is damaged beyond recovery. Indeed, in the typical case of bilateral and virtually complete cortical necrosis it is likely that, by the time the patient is admitted to hospital, irreversible renal injury has already taken place. In certain cases, seen before shock develops or becomes too severe, it may be that prompt and adequate transfusion with immediate rupture of the forewaters can forestall or arrest the spasm in the renal vessels and prevent an extension of the kidney lesions. It is not proved, but the adoption of this therapeutic approach might be one factor accounting for the apparently decreased incidence of the anuria complication in recent years. There are other reasons, of course, for encouraging rapid emptying of the uterus in cases of abruptio placentae. It is often the only way to relieve the shock, and it may prevent the onset or progress of blood-coagulation failure. But this does not mean that the majority of cases should be treated by caesarean section; this operation imposes an added stress on a patient in poor condition and, if blood coagulation is already defective, can be fatal. Incisions are much more likely to bleed than is the post-partum uterus. There is a place for the operation, sometimes in early cases when the foetus is still alive, and especially when a long and undilated cervix makes it unlikely that vaginal delivery will take place quickly. Severe abruptio placentae, however, is typically a disease of multiparae, and, contrary to Dr. O'Sullivan's statement, the cervix is partly dilated in the majority of cases when first seen. Rupture of the membranes, which should be regarded as an emergency procedure to be carried out with the greatest urgency, then generally results in a rapid onset and conclusion of an easy labour with least upset for the patient. It would be unfortunate if unsubstantiated arguments for caesarean section in all or the majority of cases of abruptio placentae led to the abuse of an operation which, while saving life in certain cases, is unnecessary and potentially harmful in others. Caesarean section can kill.

Chemotherapy and Ectopic Pregnancy.—Dr. S. R. Kamat (Penarth, Glam.) writes: After reading the answer given by your expert to the question about the relation between chemotherapy for salpingitis and ectopic pregnancy ("Any Questions?" July 18, p. 77), I thought it would be useful to recall the history of one case. An Indian woman, aged 20, developed general signs of tuberculosis in 1942. A lump was felt in the right iliac fossa and there were menstrual disturbances. A diagnosis of pelvic tuberculosis was made. The case was treated on general lines. She improved and remained well till 1947, when she gradually developed weakness, low abdominal pain, backache, dysmenorrhoea, and irregular low fever. Pelvic examination revealed swelling and tenderness of tubes and enlarged retroverted, fixed uterus. After a course of milk, tonics, etc., the symptoms improved a little. In December, 1950, she was shown to another gynaecologist, who advised exploration and ventral suspension in view of the persistent symptoms. At operation a bilateral fallopian tube tuberculosis, tuberculous endometritis, and some peritoneal tuberculosis was diagnosed and confirmed by biopsy. She was treated with streptomycin 1 gr. daily for three months, and was given rest, tonics, etc., for another year. The symptoms disappeared but recurred in a mild form in 1952. She was given a six months' course of isoniazid, 200 mg. daily empirically. She kept very well until 1954, when two episodes developed at an interval of four months. Each time there was amenorrhoea of two to four months with symptoms of gestation. Then severe pains developed and a typical episode of subacute leaking ectopics was staged. The first episode was observed, and during the second episode it was thought that tuberculosis had recurred. Tender, boggy swelling of both fallopian tubes was felt and the abdomen was explored a month after the second episode. Ectopic gestations, freshly ruptured, on the right side, and old, dead (but larger in size) on the left side, were found and confirmed histologically. Bilateral salpingectomy was performed. There was no evidence of tuberculosis anywhere in the abdomen. The patient has kept well during the last five years. This case is remarkable for five reasons: (1) Genital tuberculosis which responded only partly to prechemotherapy regime. (2) It recurred twice after six and eight years. (3) After two courses of chemotherapy it improved and there was symptomatic relief. (4) Cure was proved later, though therapy was inadequate by present standards. (5) After four years she had ectopic pregnancies on both sides, at an interval of a few months. The patient had a history of two normal pregnancies before the illness developed. Certainly in this case pathological cure has predisposed to development of ectopic pregnancies.

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